ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 17 November-December, 1959 Number 6

BUCCAL AMYLASE

Case Reports Illustrating Effectiveness in Some Hypersensitivity States

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SINCE the beginning of this decade, rather inexplicable effects have been shown to follow the parenteral administration of certain depolymerizing enzymes in humans. Such administration of carbohydrase ("hyaluronidase"),[1] proteases (tryptase,[2] streptokinase,[3] chymotryptase[4]) or a restrictive category of lipases (beef erythrocyte cholinesterase;[5] human plasma cholinesterase)[6] has resulted in a demonstrable antiphlogistic effect in areas far removed from the site of the injection. This effect of the cholinesterases was particularly puzzling since the erythrocyte-derived variety gives rise to only a transient or insensible rise in the blood concentration of this enzyme, while the plasma esterase yielded therapeutic effects even when its pre-administration plasma concentration was already elevated, as is the case in chronic allergic states.[5,7] In light of the content of this report, it is noteworthy that both types of applied cholinesterase had caused allergic hypersensitivity to abate. While such an effect might conceivably result from the "foreign protein" nature of most of the enumerated enzymes, plasma cholinesterase was derived from, and is a constituent of, normal human plasma.

Failure to adequately explain effectiveness of systemically administered cholinesterase carried over to the other mentioned enzymes. In many instances these exert therapeutic effects without any measurable absorption into the blood or tissue fluids. One reaction to the injection of some of these enzymes has been described: a rise in the concentration of

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"non-specific" or competitive depolymerase inhibitor (CDPI) in the circulating fluids.[8] It has been suggested that the use of any depolymerizing enzyme will induce this rise in CDPI[9] and that the latter is, in turn, the actual instrumentality of therapeutic response.[7,10]

More recently, a qualitatively similar antiphlogistic response has been shown to follow application of certain proteolytics to a mucous membrane such as the buccal or sublingual surface. In at least one instance, such application has been followed by demonstrable rise in the plasma titer of a CDPI; buccal streptokinase application causes rises in plasma antithrombin.[8] To further test the sequence of hypotheses in the second paragraph, Stanton and Newman first elicited the fact that injection of alpha-amylase into rats resulted in a rise in their serum "anti-amylase" titer and then utilized the buccally applied enzyme in a limited series of patients exhibiting traumatic inflammations.[11] The results, again qualitatively similar to those encountered when either parenteral or buccal trypsin or streptokinase had been employed for this type of condition, suggested a more extensive clinical trial.

Over 200 patients with a variety of overt inflammatory disorders have now been treated with buccally, sublingually or juxtalabially applied alpha-amylase. The therapeutic responses have been unequivocally favorable, and these results are subject to reporting elsewhere[11,12] The particular cases described herein indicate that this mode of alpha-amylase administration may yield, in addition, an "anti-allergic" response. Such a response has previously been elicited only with parenteral cholinesterase, though it is possible that this effect might have been forthcoming, if watched for, with the other depolymerases in common use.

Our own attention was focused on the possibility that buccal amylase might curtail allergic phenomena through an incidental observation in the "trauma" series. It must be mentioned in passing that this modality is far from an inert one; mucous membrane application of depolymerases, and particularly the one under discussion, has pronounced effects on the humoral homeostasis of the organism, of which antiphlogesis may be only one aspect or expression. This is illustrated by *Case 1* where an ostensible effect on the autonomic nervous system appeared to be produced. To best bring this out, comment will follow this case, as well as subsequently presented cases, since most of the cases overlie a common denominator in that the observations on a coincident hypersensitivity state were gratuitously obtained while the patient was being treated with buccal amylase for acute, traumatic inflammation.

REPORT OF CASES

Case 1.—A forty-four-year-old woman slipped while getting off an escalator, and sprained her left ankle. Buccal amylase was initiated within two hours of the injury when marked pain and swelling were already present. Only one tablet was given before the patient retired. The next morning there was no trace of either swelling

or immobility, and there was no pain. She was advised, nevertheless, to take an additional tablet every four hours. On insertion of the third tablet, she experienced a numbness and tingling in the last three fingers of her left hand and noticed that these digits were pale and cold. Examination showed a typical Raynaud's phenomenon over the terminal distribution of the ulnar nerve. The patient had never experienced such a reaction before. The vasoconstriction abated in two hours and no further enzyme was administered. As a test, we prevailed on the patient to resume the buccal tablets three days later; again the second tablet was followd by short and transient but definite recurrence of the same distribution of the Raynaud's phenomenon.

Comment.—This patient gave a history of hypersusceptibility to epinephrine. She had always had facial blanching and tremulousness when receiving this drug (which is usually incorporated with procaine in local anesthetics) during dental procedures. Her own dentist had learned to give her plain procaine on every occasion for this reason. There is some evidence that Raynaud's phenomenon is due to a local excess of sympathomimetic amine since peri-arterial sympathectomy has been used in its treatment. The reason for the restricted distribution of the peripheral vasoconstriction in this patient remains unexplained, but the impression that a catecholamine effect was involved led us to use buccal amylase under circumstances where epinephrine administration would have been a rational procedure.

Case 2.—A thirty-seven-year-old housewife had a history of severe house-dust allergy dating back seven years. She developed a profound rhinosinusitis (presumably on this basis) after emptying a new-type vacuum cleaner. Her protracted distress was only partially relieved by soporific doses of pyrabenzamine. Supplementation of the latter with one sublingual tablet of buccal amylase every three hours led to complete subsidence within six hours. A milder attack of nasopharyngeal congestion came on within six hours after the last dose of amylase (a total of five doses had been given up to this time) without interim dust exposure. Resumption of the amylase brought about quick relief.

Comment.—The foregoing sequence suggests submergence, rather than abrogation of the hypersensitivity state. The same would be true of the classic "anti-allergics," including epinephrine. There is, of course, no direct evidence that epinephrine release was responsible for the results in this case, *Case 1,* or any of the subsequent cases reported. Epinephrine administration could have produced these "anti-allergic" effects, but an epinephrine-release mechanism does not account for other features of the therapeutic activity of amylase; at least we are not aware that any results such as described in the next case could be due to catecholamine administration.

Case 3.—This thirty-one-year-old man showed complications of repository penicillin administration. Injection was made into the outer gluteal quadrant for an upper respiratory infection. Two days after the injection, he felt severe pain and throbbing in the injected buttock. On examination there was redness, swelling and woody induration over the entire injection site. The patient was told to go to bed and to apply hot packs since a "sterile abscess" was felt to be inevitable and would

(by all common experience) have to be subsequently evacuated. He refused this suggestion since he had to be up and around. As an alternative, he was started on one tablet of buccal amylase, with instructions to take another every four hours until told to stop.

Twelve hours later, pain and induration were much less intense. The inflamed area had shrunk to about half its original size. It seemed to be fluctuant, and the patient was told of the desirability of incision and draining of such lesions (Fig. 1). He elected, instead, to remain on the amylase therapy. All pain, soreness and inflammation were gone in thirty-six hours; a barely palpable area of non-painful induration persisted and he was told to continue the amylase, which he did for one week, stopping the medication on a Saturday.

Fig. 1. Resolving "sterile abscess" twelve hours after initiation of buccal amylase. This lesion has receded to half its initial size in this time.

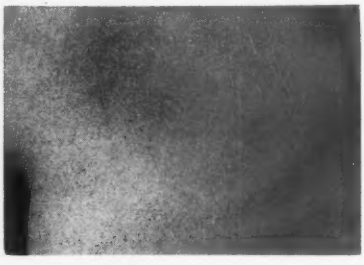

Fig. 2. Complete resolution of "abscess" and maculopapular rash commencing within twenty-four hours of discontinuance of buccal amylase.

Twenty-four hours after discontinuance of the amylase schedule, intense itching of the buttock and leg on the side of the original injection was reported. At the same time, rather severe swelling and pain of both wrists and both ankle joints developed. Examination on Monday morning revealed a completely resolved injection-lesion, but a maculopapular rash over the extremity (Fig. 2), and inflammatory arthrosis of both wrists (Fig. 3) and ankles. Re-institution of the original amylase schedule to complete abatement of the joint swelling within twenty-four hours (Fig. 4).

Comment.—This patient had had repeated penicillin administrations, both parenteral and oral, over the past seven years, having come from a country where penicillin is not a prescription item. The result illustrates what has become increasingly apparent: that no one knows when this type of hypersensitivity will manifest itself, and that a previous history of penicillin innocuity is no guarantee that some future dose will not have serious consequences. The sequence of events outlined in the case report suggests strongly that the hypersensitivity component, manifested chiefly by the arthropathy, was kept submerged by amylase administration and emerged when the latter was discontinued. The therapeutic response was reminiscent of that which has been obtained with parenteral human plasma cholinesterase. In that connection, it was impossible to show that cholinesterase nullified any "histaminic" component which might happen to reside in this type of allergy.[13]

Case 4.—This patient had arthralgia due to meprobamate administration. He was a thirty-two-year-old man who had been on Banthine therapy for periodic exacerbations of gastric ulcer symptoms. He switched to a meprobamate-parasympatholytic combination advocated for the purpose, and it did indeed control his gastric symptoms with what he thought to be less "mouth-dryness" than the previous medication had occasioned. Several weeks after beginning the meprobamate combination he began to complain of tenderness and minimal swelling of ankle and knee joints, which he attributed to the "weather." For this, he was placed on buccal amylase, one tablet every four hours. The joint manifestations abated rapidly but re-appeared on discontinuance of the amylase five days later. Meanwhile, the patient himself began to suspect meprobamate hypersensitivity as the basis for the arthralgia and returned to Banthine maintenance with relief of the joint symptoms. A day's trial of meprobamate (1.6 gm) was followed a day later by a severe recrudescence of the joint symptoms which again subsided within twelve hours after resumption of buccal amylase. The latter was then discontinued three days later without incident.

Comment.—This, like *Case 3*, represents submergence of an allergic reaction even though the presumed allergen was still extant.

Fig. 3. Arthrosis of wrists and hands on cessation of buccal enzyme therapy. Same time as Figure 2.

Fig. 4. Subsidence of Arthrosis twenty-four hours after recommencing buccal amylase therapy.

Case 5.—This was a twenty-eight-year-old man who "bruised easily" and who had once, during childhood, had a diagnosis of "allergic purpura." There was definite history of penicillin and pineapple hypersensitivity. The patient turned his ankle and wrenched his right knee in a fall, striking his right shoulder in the process. On examination, there was swelling of the ankle and knee; the left shoulder joint, though tender at the site of the subdeltoid bursa and painful on motion, exhibited no externally visible abnormality.

Buccal amylase was started on the evening of the day the injury was sustained and the patient told to continue dosage at three-hour intervals. The following morning all pain and limitation in all joints were gone, but the amylase was continued. That evening an ecchymosis became visible in the posterior axillary fold of the injured side; this, the patient remarked, was already greenish in color rather than the bluish extravasations to which he was accustomed with a day of injury (greenish discoloration usually takes three to five days from the time of extravasation).

Comment.—This case was detailed because the apparently rapid degradation of extravasated hemoglobin suggests an augmentation in activity

of the reticulo-endothelium system. The possibility of such a stimulation of this cellular immunity system is not incompatible with current proposals concerning the mode of action of systemically administered depolymerizing enzymes.

Case 6.—A thirty-one-year-old man with a history of sciatica who, during military service in Korea was said to have had a herniated disk, had had no difficulty for the past five years, during which time he avoided lifting heavy objects. He had purchased a new home and carried his wife over the threshold, waiving the interdiction. The next day he was immobilized with severe back pain radiating to the legs. He tried aspirin, which eased the pain, but caused nausea and pyrosis.

Buccal amylase was started on the second day of invalidism with slow but steady amelioration of the backache over the next four days. This may have been coincidental. However, the patient noticed that a troublesome and persistent catarrhal otitis externa which had been with him for three years and which had completely resisted all modes of therapy, had "dried up." Curiously enough, with forty-eight hours of discontinuance of the buccal amylase (on the seventh day) when the back and ear troubles had both abated completely, there was slight recurrence of the backache and the otic canals were again moist and itchy. Both conditions again responded to buccal amylase (one pellet thrice daily) on which the patient has elected to remain.

Comment.—The obvious question that arises concerning the incorporation of this case in a "hypersensitivity" series has only the incomplete answer that external otitis is so frequently of covert allergic origin that this case is so presumed.

DISCUSSION

As is evident from the nature of the reported cases, this does not represent a definitive attempt to evaluate the usefulness of buccal amylase therapy in allergic conditions. The results observed occurred coincidentally in a larger series which had another purpose. However, the results appear to have implications of some importance.

The popular explanations of anti-inflammatory effects of buccally applied depolymerizing enzymes are based on one or the other of alternative assumptions: (1) that the applied enzyme itself is directly absorbed through the vascular channels underlying the mucous surface or (2) that plasminogen in saliva is activated to plasmin which is thereafter absorbed as such. Either the applied proteolytic, or plasmin, can then act to dissolve a "fibrin barrier" which walls off an inflamed area and which is supposed to prevent absorption of the inflammatory exudate. There are some deficiencies in the system of hypotheses proposed. All the proteolytics in use, as well as plasmin itself, are of rather large molecular size, rendering their diffusion through oral mucous membranes questionable. The role of a fibrin barrier is speculative; we have no evidence that patients with congenital fibrinogenopenia do not react to trauma by the classic inflammation sequence. The effectiveness of alpha amylase (which has a molecular size of about 60,000) contradicts both

parts of the hypothetical chain, since it is neither plasminogen-activating nor does it have direct fibrinolytic properties. These properties are likewise absent from chymotrypsin, which is also "anti-inflammatory."

A more useful explanation of the results of systemic enzyme administration is that these results are actually due to a compensatory elaboration of CDPI. Antidepolymerases of the competitive class seem to be heparinoids,"[14] if not heparin itself.[18] Compensatory production of the macroanionic heparin is believed to be a dynamic homeostatic reaction when certain macrocations are exhibited.[15] In this connection, it must be recalled that all enzymes cited in this report are potentially macrocationic since they contain electrostatically active portions referred to as "anion-binding sites." These sites must, of necessity, be of opposite charge from the groups which they bind.

Paradoxically, it has been known for some time that a qualitatively similar anti-inflammatory effect could be obtained whether one applied the macrocationic enzymes, or their opposite numbers, the macroanionic heparinoids, either locally[16] or systemically.[17] And if, as Glick and his co-workers have maintained, the physiologic macroanion concerned in depolymerase inhibition is identical with heparin,[18] we may arrive at more satisfactory explanations of the therapeutic events following enzyme application. In the first place, one need not assume transposition of the applied enzyme across a mucous membrane. The application of the macrocation could engender electrostatic changes in the mucous gland cells (known to be electrically polarized) and this could, in turn, cause discharge of heparin from the profusion of mast-cells of the capillary bed underlying these glands.*

In addition, the heparinoid macroanions have broad systemic potentialities and these appear to actively manifest themselves when their concentration is substitutively or autochthonously raised. Most pertinent to present discussion is their chemical configuration as antibody-type haptenes which can combine with (and nullify the activity of) antigens.[19] This may in part explain the anti-allergic action typified by the case reports. But the immunologic consequences are probably even broader. For instance, it has been shown that, along with the elaboration of CDPI, the injection of trypsin or amylase into rats results in a rise of both complement (properdin?) level and opsonic index,[12] that is, the enzyme itself, or its compensatorily elaborated inhibitor enhances certain phases of both cellular and serophytic immunity reactions. Studies in progress seem to allocate this action to the inhibitor.

The immune responses mentioned are opposite to these evoked by 11-oxysteroid (glucocorticoid) administration even though the latter also

*Since the mast-cells are reputed to release serotonin as well as heparin, the vasoconstrictor effects recorded in *Case 1* from buccal enzyme administration might conceivably have been due to this pressor substance rather than the catecholamine as suggested in the comment. The point is speculative but is nevertheless mentioned as in keeping with the proposed mechanism of buccal enzyme activity.

has pronounced anti-allergic and anti-inflammatory effects. It is pointed out in this connection that the glucocorticoids are also depolymerase inhibitors though this action on their part (unlike the heparinoids) is noncompetitive. Various other differences in the end results of 11-oxysteroid and enzyme administration will be brought out in future discussion; here we will say that the realm of enzyme therapy may prove to be as wide as that of steroid therapy.

The systemic exhibition of enzymes (as distinguished from their ingestion or topical application which, admittedly, goes back to remotest antiquity) is thought to be a new departure in therapy. However, a scrutiny of the literature indicates it to be better than half a century old. Its rationale in all instances was to augment a supposedly deficient supply of autochthonous enzyme so that a specific function of the enzyme could be carried out. In other words, the goal of enzyme therapy was substitutive. Trypsin was known to digest fibrin. Hence trypsin was injected to dissolve a thrombus or the barrier confining inflammatory exudate. One of the writers, finding an inordinately low blood cholinesterase to characterize acute leukemia, administered this enzyme to raise its blood level. The acute leukemic patients were only equivocally benefitted, but altogether unanticipated and unequivocal therapeutic results accrued. Allergic dermatoses, in which the blood cholinesterase was already elevated, responded inexplicably.[6] And this response extended to sustained or chronic penicillin sensitizations as proved to be forthcoming from a non-esterase type of enzyme, amylase. There have been several reports on the use of penicillase[20] for this specific type of sensitization on the assumption that a substitutive rise would destroy any residual penicillin which maintained the hypersensitivity state. And results seem unquestionably to be forthcoming. But is it on the basis of the assumption? In light of the reports on cholinesterase and on amylase in this connection, there is now some doubt that penicillase acts in a "specific" manner at all. The enzyme, like other proteolytics is an amidase which breaks an acid-amide linkage and converts penicillin to penicilloic acid. But it now appears that either an esterase or a glycosidolase, neither of which can disrupt such a linkage, will accomplish the same end result *in vivo*. Evidently our theories of the mode of action of systemically administered enzymes will need constant modification as the art progresses.

SUMMARY AND CONCLUSIONS

Concordant with the results obtained from buccal administration of other depolymerizing enzymes (such as trypsin or streptokinase) the mucous membrane application of a carbohydrase (alpha amylase) is followed by antiphlogistic effects at inflamed sites elsewhere in the body. The case histories of some patients who showed a coincident alleviation of presumed allergic manifestations while the enzyme was being employed,

are detailed with comments. The effect described consists of a submergence, only, of hypersensitivity phenomena which are liable to recur on withdrawal of enzyme therapy.

While several explanations of the effects of systemically exhibited depolymerizing enzymes have been proferred, none is entirely satisfactory. The most acceptable current explanation is that a compensatory rise in circulating, competitive antidepolymerase is evoked and that this type of inhibitor, which is usually heparin, or a heparinod, is the actual anti-inflammatory or anti-allergic agent operative when enzymes are administered.

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Submitted April 7, 1959

REHABILITATION OF CHILDREN WITH INTRACTABLE ASTHMA

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THIS paper will present the development of the program for the rehabilitation of the asthmatic child in the Southwest area which has been popular for many years as a health center. The rehabilitation of asthmatic children and adults began a long time ago before the term "rehabilitation" became popular or before extensive programs were developed. The word "rehabilitation" comes from medieval Latin meaning restoration of one's health and efficiency. The term has been used quite extensively in the sense of restoring a person, such as a disabled soldier, to a status of independent earning power through long vocational lines. Climate has played a great role in the early picture of the rehabilitation of the asthmatic in this area.

The Southwest, of which Tucson is a part, has been a health center for many years. Many of us can remember the time when the standard treatment for tuberculosis was to send the patient to the Southwest. Of late years, patients suffering from arthritis, sinus disease, bronchiectasis, asthma, and other allergic conditions, have found their way to this area for the relief of their afflictions. Many come for the health-giving properties of the climate, others to escape the rigors of the climate in their home areas, and still others just to enjoy the climate.

Climatotherapy in the treatment of disease is by no means new. Galen* sent his tuberculous patients to Tabia near Vesuvius, and Celsus* recommended a long sea voyage. Hippocrates* observed many years ago "It is changes that are chiefly responsible for diseases, especially the greatest changes, the violent alteration both in seasons and in other things, but seasons that come on gradually are the safest, as are gradual changes of regimentation and temperature."

In Tucson the seasons merge one with the other gradually and there is not the storminess or violence present which is found in other parts of the country. During the period when climate had its great vogue in treatment of chronic disease, schools were established in the Southwest, and many asthmatic children and children with other chronic diseases found their way into these schools. Most of these children overcame their asthma or controlled it to such an extent that they were able to finish their education. Some remained in the Southwest and others returned to the East and Midwest or other parts of the country.

Presented at the Sixteenth Annual Congress of The American College of Allergists, San Francisco, California, March 18, 1959.

*Quoted by Stevenson.[1]

During this period considerable literature about the Southwest climate and its role in the treatment of chronic disease increased considerably.

REVIEW OF LITERATURE

Stevenson,[1] in discussing the climate of Arizona, felt that an ideal climate is one which enables people to be out of doors as much as possible. He pointed out that the southern part of Arizona has abundant sunshine, great warmth, little precipitation, low humidity, comparatively stable barometric pressure and slight storminess. He considered that southern Arizona had a basically stable climate. A striking effect of the low humidity is the lability of daily temperatures. Heat is largely derived from direct radiation of the sun, but the ground retains little heat and cools rapidly at night. This nocturnal cooling effect provides pleasant relief from the often excessive warmth of the day in summer.

Mills[2] pointed out that it is in the stormy winter season and in the storm regions of the earth that respiratory and rheumatic infections most severely afflict mankind. At no time of the year do major storm centers pass over the southwestern part of the United States, of which Tucson is a part.

Baldwin[3] reported on sixty-two patients in 1944, all of whom were known to have been in Arizona not less than four years. Forty-four per cent had been completely relieved of asthma for two or more years. Patients will benefit most whose disease has been dependent upon climatic violence and associated respiratory infections. The patient should fully understand what he is to expect from the climate and what he must contribute to the attainment of his health.

Cook[4] stated that children with recurrent infections certainly do better in regions where they may run and play outdoors, avoid sharp changes in weather and get a maximum of sunshine.

L. T. Tuft[5] thought that asthmatic patients are more comfortable where the temperature is high but even, and the humidity low.

Unger[6] felt that climate is overrated and that many patients are sent to other areas when removal of the irritating substance at home would have given better results. He felt that great care should be taken to study the patient before a move was suggested.

Metzger[7] felt that the allergic patient presents a highly individual problem. Changes of climate should be predicated on the knowledge of sensitivities of the patient as well as the distribution of allergens and also the suitability of climate to the patient. Unless these things are done, he felt that justice was not being done to the patient.

Smith[8] has quite an extensive monograph on the climate of Arizona and discussed it very thoroughly, especially with regard to all its factors of latitude, altitude, mountain ranges, remoteness from bodies of water, and rainfall.

Peshkin[9] in 1930 reported on a study of asthma. He felt that the im-

portant thing in treatment of children with asthma was separation from home (parentectomy). He felt that climate played no role in the treatment of this condition. In answer to his plea, the Jewish Home for Asthmatic Children was established in Denver in 1940. Peshkin and Abramson[10] at the First National Seminar of Regional Medical Consultants, reviewed the development of the Jewish National Home for Asthmatic Children and its operation at the present time.

In 1957 H. S. Tuft[11] reported on the Jewish National Home for Asthmatic Children. He stated that in 500 children between the ages of five and fifteen years, 50 per cent were free from asthma upon or a few days after admission and had no further asthma during their stay.

Gottlieb,[12] in his review of climatotherapy and institutional care, refers to Hallowitz's report on the benefits of residential treatment at the Jewish National Home for Asthmatic Children in Denver which contends that many of the benefits stemmed from separation from the family and home environment. Gottlieb also refers to comments by Huet from the Netherlands that two-fifths of a series of asthmatic children remained free from asthma after entering the Asthma Center in the Netherlands. These apparently were milder cases.

Marks[13] sent out questionnaires to pediatricians and allergists in the state of Florida and also to out-of-state specialists. Among the out-of-state specialists there was a division of opinion concerning the therapeutic value of climate. The Florida pediatricians and allergists felt that children who came to Florida improved to a certain point, but that the improvement depended upon the type of existing allergy. It was believed that improvement in southern Florida was largely due to the reduced incidence of upper respiratory tract infections as well as freedom from northern pollinosis. In the last analysis, every allergic child must be managed on an individual basis.

An editorial[14] in the *Journal of Allergy* points out that despite the progress in treatment of asthma, one of the oldest approaches to the problem, change of climate, remains popular. As in the past when Egypt was recommended as an ideal winter climate, so Arizona is often suggested for the asthmatic patient today. Although climatotherapy falls short of universal efficacy, the editorial points out that such persistent popularity must have a basis of fact. That there is a real need for the care of asthmatic patients of limited means in areas of good climatic conditions (such that people making a change of climate may do so on a trial basis) is self-evident. There is a plea made hoping that more sanatorium beds for the treatment of tuberculosis may be available for treatment of asthma.

Klotz and Bernstein[15] discussed environmental therapy in bronchial asthma and point out the various factors to be considered in determining whether an environmental move should be made.

An editorial[16] considers the subject of people going to a dry, warm climate in a high altitude especially for the treatment of chronic intractable

asthmatic bronchitis associated with bronchiectasis and paranasal sinusitis. It points out that every year there are more people arriving in areas of Arizona and New Mexico, and further points out that it is essential to determine whether this new climate will indeed effect an improvement so that these people may go into these new communities without becoming a ward of local charity. It is especially important to recognize if the patient will *not* benefit from a change of climate.

Sherman and Kessler[17] feel that the greatest benefit to be expected from change of climate is in severe infective asthma associated with chronic upper respiratory infection, particularly hyperplastic sinusitis, and that children who have done poorly in cold wet climates are more often improved by attending school in the West or Southwest for a year or two so that on their return they are sufficiently improved in general health to tolerate their home climate.

NATIONAL FOUNDATION FOR ASTHMATIC CHILDREN

Formation

Several years ago the management of one of the private schools near Tucson, which provided a place for children with asthma, began to think in terms of a Foundation. In the course of time a plan was evolved to provide a place where asthmatic children from families of low income could be sent for treatment. In 1954 the National Foundation for Asthmatic Children started its program for the rehabilitation of asthmatic children at the Sahuaro School near Tucson. The School was to provide a program for the rehabilitation of children with intractable asthma. It would combine all known means and methods of treatment in a setting with a home atmosphere in group living. Intractable asthma is defined as perennial asthma which does not respond to the conventional forms of treatment in the child's home community and also asthma which needs steroids for its control. Only children meeting these requirements are accepted.

Principal Features Which Distinguish the School

Climate.—Climate, in the past and at the present time, is one of the important phases in the treatment of the asthmatic child in the Southwest. Factors which are essential to an ideal climate are found in Tucson:

1. Outdoors as much as possible
2. Abundant sunshine
3. Great warmth
4. Little precipitation
5. Low humidity
6. Comparatively stable barometric pressure
7. Slight storminess
8. Gradual seasonal changes

Tucson presents a climate with maximum amount of sunshine and minimum relative humidity, very little rain and very little wind. Normally, the barometric pressure is stable. The pollen count is low. The winters present many warm, sunny days. Although the temperature appears high in the summer, the relative humidity is low, the evaporation factor is high, and there is enough range in temperature to afford comfortable nights.

Education.—The Sahuaro School is the only school of its kind which provides educational facilities on its grounds for the first eight grades. We feel that it is much better to provide education for these children at the school. It enables us to keep the children together and spares them the problem of competing with well children in the public school system. We want as much as possible to make them forget that they have asthma and we do not want them to be brought in contact with well children at this time. We would like to have them become well and happy in their way and become strong enough to meet the competition of the world later on.

Individualized Medical Treatment.—The program for medical care is individualized to the child's particular needs. Internists, allergists, pediatricians, psychiatrists, psychologists, dentists, and social workers are provided for the care of the child. A group of consultants in other specialties provide additional care as the need arises. Each child is carefully examined. The plan of treatment is carefully worked out to meet the individual needs of each child. Some children may need little, if any, treatment—they go to school, live in the cottages and receive medical attention such as normal children receive as the occasion arises. Other children have to have a more extensive program—many need specific injection therapy following skin testing, various sorts of symptomatic medicine, and others have to be treated with steroids from time to time. Still others may need psychiatric and psychological guidance.

Change of Environment.—Change of environment has always been an important part of treatment throughout the years. There are many factors in change of environment other than taking the child away from his home and putting him in a new area. Removal of the child from home changes many conditions found in the house or in the territory about the home. The removal from one school to the school in Arizona results in leaving many factors and probably finding new ones. The climate of course, strictly speaking, would have to be considered under environment. Seasons, temperature changes, geographic location and atmospheric changes, all play a part in the problem. It is not wise to consider that the only advantage in changing environment is parentectomy. If nothing more, seeing a different world through the same pair of eyes is very important.

Recreational activities.—Recreational activities are important at the School. The yearly mild climate makes it possible for the children to play outside most of the time and provides for a varied and extensive recreational program. Very few of the children are able to engage in group recreation at home, but at the School most of them are able to participate in swimming, dancing, baseball, basketball, running and other group games. Swimming is one of the most popular forms of recreation. Singing and breathing exercises help to promote diaphragm function. Activities such as trips to the mountains, picnics and visits to the Arizona Sonora Desert Museum are all included. Social activities are fostered to provide group activities such as The Boy Scouts, Girl Scouts, stamp clubs, entertainment committees, and other club or group activities.

Admission Procedure

Our first contact with the asthmatic child is usually through the family doctor who in most cases sends in the medical report. Regional allergy consultants throughout the United States co-operate in screening children for the School. No child is accepted until he has been certified by a regional consultant. A number of children who have been examined have been found not to have had the advantages of thorough, consistent and continuous treatment in their own locality, and have been refused admission. The application must be from a family of low income and must include a social service report from a private or public social welfare agency. These agencies have co-operated in helping the families while the child is in the School and have been invaluable in helping the child readjust himself to his home upon return from the School. In some instances the child has developed insight into the problem and has been able to help in the rehabilitation of the family (parentectomy in reverse). Children from six to twelve years of age are admitted. Lack of facilities prevents the addition of other age groups.

Physical Plant

At this time I would like to include some information about the physical plant of the School. It has a beautiful location approximately six miles east of town on a ten-acre tract of land in the desert surrounded by mountains; to the north the Catalinas tower some 11,000 feet and other ranges on the east, south and west, form an inter-mountain plain.

There are thirteen buildings, including five dormitories or cottages for the children which provide accommodations for about sixty-five children. Ten to twelve children, depending on the age group, are assigned to each dormitory with either a house mother or a house father. Part of the administration building provides dormitory space for some of the older girls. The dining hall with an attached modern kitchen provides meals at one sitting for all children. The hospital provides ten beds and there is an adjoining completely furnished clinic. There is an Arts and Crafts

Building. Recreational grounds occupy more than half of the area with recreational fields for football, baseball, volleyball, and shuffleboard. A large swimming pool provides additional recreation throughout the year. Separate buildings provide facilities for a modern, up-to-date school from the first through the eighth grades. Lack of plant facilities precludes the provision of other grades for a wider age group. Arrangements are made for the children to attend the church of their choice.

RESULTS

Our children are all asthmatics of the perennial type with many factors involved in their chronic conditions. They are by admission policy intractable cases of asthma. Our studies do not indicate any more emotional problems for this group than for a normal group of children. Psychological tests which have been performed on our children would indicate that a majority were above the normal range. Figures were obtained to show:

1. General results
2. Percentage of absenteeism from school
3. Number participating in group recreation at the School as compared with home.

General Results.—The years of operation and the number of children who have been at the School are few in number; yet it is of interest to review the results which have been achieved.

TABLE I. RESULTS WITH 141 CHILDREN

Improvement	
Excellent	44.6 per cent
Moderate	19.1 per cent
Fair	29.6 per cent
No improvement	6.3 per cent
Deaths	1 child

The percentage of absenteeism for the School during the four years considered is better, except for the year 1957-58, than that for the public school system of normal children.

TABLE II. SCHOOL ATTENDANCE

Schools	Students	Days Present	Days Absent	Percentage Absenteeism
1954-55				
Sahuaro School	38	5,019.5	301.5	5.666%
Pub. School Dist. No. 1	21,453	3,097,997.5	199,092	6.038%
1955-56				
Sahuaro School	42	6,102	222	3.510%
Pub. School Dist. No. 1	23,893	3,465,304.5	237,876	6.423%
1956-57				
Sahuaro School	55	7,360	289	3.778%
Pub. School Dist. No. 1	25,835	3,755,419.5	236,460.5	5.923%
1957-58				
Sahuaro School	72	8,580	774	8.274%
Pub. School Dist. No. 1	27,501	4,009,946	311,287	7.203%
Sept. 1958				
Sahuaro School	53	1,106	7	0.628%

More children are able to participate in group activities at the School than at home as indicated by the figures for the various types of recreation.

TABLE III. ACTIVITIES FIGURES
(GROUP RECREATION)

Activities	At Sahuaro School 1958	At Home
Playing games	51	29
Roller skating	44	29
Dancing	46	26
Swimming	50	28
Baseball	33	29

CONCLUSIONS

We feel that the program at the Sahuaro School of the National Foundation for Asthmatic Children, based on climate, individualized medical care, change of environment, educational program, and recreational facilities at the School, has resulted in a very workable plan for the rehabilitation of the asthmatic child.

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Submitted April 14, 1959

ALLERGY AND RECURRENT EPISTAXIS IN CHILDREN

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NOSEBLEED is of such common occurrence that few people reach adult life without having experienced epistaxis from one cause or another. The majority of nosebleeds are mild in nature and usually cease as abruptly as they start, so that the emergency status of this condition is a relative one. Often the bleeding has ceased before the patient is seen by the physician.

Repeated epistaxis is usually not a serious condition in children, but it can be a source of great annoyance to the physician and can be alarming to the small patient, and, of course, is of great concern to the parents. There are times when repeated epistaxis can result in depletion of the blood volume to a serious degree, requiring blood transfusion. The greatest majority of nosebleeds in children are of the anterior type and, fortunately, are easily controlled by simple local measures.

Much has been written concerning the etiology and control of nasal bleeding and apparently there is no common denominator for this condition. There is quite a difference in the recurrent nasal bleeding in children and a similar episode in adults. In adults, the bleeding is frequently posterior and not easily approached for control. The hemorrhage is often the result of arteriosclerotic change in the vascular bed, a situation not encountered in children. It has been suggested that spontaneous epistaxis may be due to a reduction in circulating blood estrogens which, if true, would be a debatable factor in the younger age group.[1] "Deficiencies in the clotting mechanism of the blood are seldom contributing factors in nasal hemorrhage" despite the many preparations offered by the pharmaceutical houses to correct these defects and control nasal bleeding.[2]

A review of the literature on this subject would lead one to conclude that spontaneous epistaxis has not been satisfactorily explained. In consulting the leading textbooks of pediatrics concerning recurrent epistaxis in children,[3-5] they are all agreed that it is a commonly encountered condition in the practice of pediatrics and that the bleeding is usually anterior and easily controlled. Many of the textbooks state that the hemorrhage results from ulceration of the septum in Little's area. However, no mention is made as to what might be the etiology of these nasal ulcers. It has been my observation that ulcers of the nose are not too common in children unless the septum is deflected, presenting a dry area of mucous membrane with secondary infection and ulceration. Little or no mention is made of allergy as being a possible factor in the etiology of epistaxis

Presented at the Sixteenth Annual Congress of The American College of Allergists, San Francisco, California, on March 19, 1959.

in children. Usually the patient is considered to be "subject to frequent nosebleed." This naïve explanation seems to be completely satisfactory to all concerned.

Schwartz[6] has stated that, "Eliminating trauma and blood dyscrasias, nosebleed in children is more often associated with allergy than any other disease."[7] In a survey of all cases of epistaxis admitted to Barnes Hospital and Childrens Hospital in St. Louis between 1928 and 1942, 50 per cent of cases in the children's group were associated with acute rheumatic fever and inactive rheumatic heart disease. The incidence of allergy in rheumatic patients is two to three times greater than in a similar group of controls.[8] On the strength of these unrelated observations one might conclude that there is more than a casual relationship between epistaxis in children and allergy.

The pathologic changes in the respiratory system as a result of allergic involvement comprise smooth muscle spasm, increased capillary permeability, tissue edema, and increased activity of mucous and serous glands. The decrease in the ciliary action of the overloaded mucous membrane interferes with the normal protective function of the respiratory epithelium.[9] As a result of the incomplete antibacterial and cleansing action of the respiratory mucosa, an ideal soil is prepared for the uninhibited growth of pathogenic bacteria.[10] Edema and excess mucus interfere with the normal drainage.[11] The damage to the nasal epithelium through the excessive drying and crusting of overabundant nasal secretions reduces its protective value, making the capillary bed of the nose more accessible to trauma. Although the tissue changes in the nose more or less parallel the severity of the symptoms, there are many instances, particularly in children, in which this is not so. Gross edema and polyps are rare before the age of puberty. Although capillary dilatation and permeability, smooth muscle spasm, and tissue edema are the usual findings in allergic disease, the physician dealing with the young allergic patient must be prepared to recognize these signboards of allergy in all their modifications and distortions.[6] Allergic reactions are usually characterized by rapid onset, violent course, and slow regression, but in the younger patient nasal examination in respiratory allergy may show little more than a slight increase in the nasal secretion. Allergic involvements of the upper respiratory tract in children are very often overlooked unless accompanied by other more definite signs of allergic disease elsewhere in the body. Evidence of nasal obstruction may be constant or intermittent. There may be brief attacks of nasal blocking with long periods of remission at which time the nasal mucosa will be normal in appearance. The discharge may be profuse or watery, or may be entirely postnasal and will not be detected by casual examination unless the nasopharynx is inspected. The secretion may be dried to crusts, particularly during the winter months, due to the decreased humidity in our homes and school-rooms where the solution

to the problem of proper humidification is not adequate in our modern heating systems.

Sudden, unexpected, and unexplained bleeding from the nose of a child who seems to be in good health is the outstanding symptom of this condition. The bleeding seems to come for no apparent reason. Usually there is no local trauma to precipitate the bleeding or the trauma is so slight as to be completely overlooked or discounted, such as rubbing the nose, washing the face, turning over in bed, et cetera. Often the bleeding is slight and can be controlled by simply pinching or applying pressure to the nose. At times, the bleeding will cease as abruptly as it started, only to recur in several hours. Repetition of these hemorrhages may continue for several days and cease entirely, but return in several weeks, or even months. Frequently the only evidence of bleeding will be blood-stained bedclothing resulting from bleeding during the night while the patient is asleep. On occasion, in small children, the bleeding may follow the posterior route to the nasopharynx and be swallowed, so that the first evidence of bleeding will be the vomiting of ingested blood or the passing of blood by stool.

The severity of bleeding and the time between these attacks is extremely variable. There are no doubt many cases where the bleeding is precipitated by picking or fussing with the nose, despite the vehement denials of the parents, particularly in those children where nasal allergy results in an itching and irritated nose. At times, the episodes of bleeding will follow a pattern of occurrences during the Winter months, or during the Spring or Fall of the year, coinciding with a house dust or pollen allergy. At times the bleeding will coincide with the eating of certain foods.

In most of these cases labeled spontaneous epistaxis, no cause for bleeding is evident on superficial examination. After the bleeding has been controlled, however, a careful history and examination will often reveal some signs of allergic involvement. In those cases where the nasal mucosa presents unmistakable manifestations of nasal allergy the physician then has only the problem of searching for the offending allergen. In many of the cases showing no apparent nasal pathology, a more detailed search will often reveal some excess nasal discharge, and cytologic study of the secretion may be very suggestive of an underlying hypersensitivity. At times when there is very little evidence of allergy in the nose, physical examination may reveal signs of allergy elsewhere, such as the presence of excessive lymphoid islands on the posterior pharnygeal wall,[12] evidence of eczema, fissures at corners of the mouth, and so forth. A careful history may uncover probable allergic disease in the past, such as infantile eczema, colic, attacks of croup, frequent head colds, and bronchitis, or a definite history of allergy in the immediate family. Many of these patients must be seen several times before a suspicion of allergy can be substantiated by physical findings, skin tests, and laboratory studies.

It is not the intent of this presentation to deal with methods of control

of nasal hemorrhage in children, but rather to point out that so-called spontaneous or recurrent epistaxis may be an early manifestation of allergy, and that the control of a single episode of bleeding is inadequate. In every case of repeated epistaxis in children, in the absence of a definite cause of bleeding, such as blood dyscrasia or gross local pathology, a careful search for allergic disease should be made. Once the diagnosis of allergy is suspected, a complete history and physical examination with adequate skin testing should be carried out.

TABLE I. ALLERGY AND RECURRENT EPISTAXIS IN CHILDREN

Total number of cases	60
Period of observation	2-5 years
Female	32
Male	28
Age at onset of epistaxis	1-10 years
	(average—4.5 years)

This study comprises a group of sixty children under observation for a period of two to five years. The group of cases consists of thirty-two girls and twenty-eight boys. The age at the time of the primary epistaxis was from one to ten years, with the average age at the onset of epistaxis being four and one-half years. In all cases, complete physical examination and laboratory studies of the blood revealed no gross pathology, blood dyscrasias, nor defects in the clotting mechanism of the blood to account for bleeding. All the children in this study experienced recurrent episodes of epistaxis three or more times during a twelve-month period.

TABLE II. ALLERGY AND RECURRENT EPISTAXIS IN CHILDREN

	Cases	Per cent
Presenting definite allergy	18	30
Developing allergy 2-5 years after onset of epistaxis	15	25
Considered suspicious of allergy by history	11	18.33
Total	44	73.33
Showing no evidence of allergy	16	26.66

In this study, eighteen, or 30 per cent, showed definite allergic disease at the time of the initial onset of epistaxis, as evident by typical allergic findings on physical examination, cytologic study of the nasal secretions, skin testing and elimination diet. A total of fifteen, or 25 per cent, developed allergic disease in two to five years after the onset of epistaxis. There were eleven cases, or 18.33 per cent, in this study that were considered to be very suspicious of allergic disease by a history of past allergic manifestations, or a history of definite allergic disease in the

immediate family, so that, in this study there were a total of forty-four cases, or 73.33 per cent, who experienced recurrent nasal bleeding and presented a direct association with allergy.

There were sixteen children, or 26.66 per cent of this group who presented no evidence of allergic involvement nor gave any history of past allergic disease or a family history of allergic disease. It must be remembered, however, that this study comprises a group of children under the age of ten years, so that it is entirely possible that a considerable number of these children may develop allergic disease at a more advanced age.

In the treatment of these cases following primary control of the nasal hemorrhage, all allergic patients treated by the control or desensitization to the offending allergen showed improvement as evident by a decrease in the number and severity of attacks while under treatment. In all cases where allergic symptoms were considered minimal by the parents, antihistaminic medication resulted in definite improvement.

Early management of mild allergic disease in children could very well prevent more serious disease, such as asthma, that could develop at a more advanced age. Allergic disease is very often present in an obscure and not easily recognized form in early life. Much can be done to prevent serious consequences by the early recognition and management of allergic disease in these young patients. Repeated spontaneous epistaxis is often an early allergic manifestation in children and careful search will usually bring the offending allergen to light.

SUMMARY AND CONCLUSIONS

Recurrent epistaxis in children is commonly encountered in the practice of medicine.

Careful study of these cases will often reveal an underlying allergy to be the one constant factor to be considered in the etiology of this condition.

Repeated epistaxis in children is often a very early sign of allergic involvement and may be followed in later years by more serious allergic disease.

In all cases of recurrent epistaxis in children a thorough search by history, physical examination, and laboratory studies should be carried out, not only to decrease the episodes of nasal bleeding, but to prevent the development of more serious allergic disease in later life.

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Submitted April 2, 1959

"PRIMATENE" SALES CURBS CONTESTED

Arguing that state labeling regulations cannot take precedence over a ruling of the federal government, Whitehall Laboratories has gone before the Pennsylvania Supreme Court in an effort to have its "Primatene" asthma remedy admitted into this state for over-the-counter sales.

The Whitehall suit resulted originally from a 1956 ruling of the State Health Department which held that the product contains a habit-forming drug, phenobarbital, and therefore may be dispensed by prescription only. Under Pennsylvania regulations, phenobarbital requires a warning label, but, Whitehall pointed out, the federal government has already ruled the medicine exempt.

Company counsel, arguing the case here, alleged that the state's position if upheld, would mean that federal authority on drug control questions could be wiped out by decisions in each of the states. Earlier, Dauphin County (Harrisburg) Court had refused Whitehall's request for an injunction to set aside the state health department ruling. The Pennsylvania Pharmaceutical Association has filed a "friend of the court" brief.—From *Drug Trade News*, 34:28 (June 15), 1959.

DURATION OF EFFECT OF A SUSTAINED RELEASE MIXTURE OF ANTIHISTAMINIC AGENTS: TRIDECAMINE

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THE object of this study was to determine the duration of effect of a new sustained-release mixture of three antihistaminic agents, Tridecamine,* and to compare its *in vitro* dissolution rate and *in vivo* duration of action with two other physical types of gradual-release antihistamine dose forms.

Each of the component antihistamines of Tridecamine is well established in the symptomatic treatment of allergy and each belongs to one of the three major clinical groups of antihistamines.[1] The chemical structure of each compound is illustrated in Figure 1.

The antihistaminic constituent of Tridecamine are incorporated in a special table base, designated as Dospan,** which provides a constant, gradual release of medication over a prolonged period. Antihistamine A is a repeat-action tablet designed to provide step-wise release of medication. Antihistamine B is a capsule containing coated granules designed to provide slow, continued release of medication.

Early clinical reports from one investigator[2] indicated that the duration of action of Tridecamine was indeed prolonged, even as much as twelve to twenty-four hours in some patients. It was evident that correlation of *in vitro* dissolution rate with *in vivo* duration of action was necessary for proper selection and control of disintegration rate and time.

METHODS AND RESULTS

In Vitro.—Disintegration rate of Tridecamine Dospan, Antihistamine A and Antihistamine B, was determined by measuring the rate of release *in vitro* in artificial gastric and intestinal juice using the U.S.P. (Stoll-Gershberg) tablet disintegration apparatus. This apparatus was modified so that the basket would retain the Antihistamine B coated granules. This was accomplished by replacing the bottom screen with 30 mesh stainless steel screen and sealing it tightly to the base with low-melting polyethylene. A similar screen was sealed to the top of the basket. U.S.P. XV Simulated Gastric and Intestinal Fluids, kept at 37° C. in a constant temperature bath, were used throughout the tests.

Twelve tablets (or capsules) were placed in each basket and the basket

*Tridecamine is the trademark of The Wm. S. Merrell Company, Cincinnati 15, Ohio, for a combination tablet containing 20 mg. each of doxylamine succinate, pheniramine maleate, and pyrilamine maleate.

**Dospan is the trademark of The Wm. S. Merrell Company for the special sustained-release base.

was lowered into an 800 ml beaker containing 600 ml of Simulated Gastric Fluid at 37° C. The apparatus was then operated in the prescribed manner. At the end of one hour the beaker was removed, the basket carefully drained, and the volume adjusted to 600 ml. An aliquot was

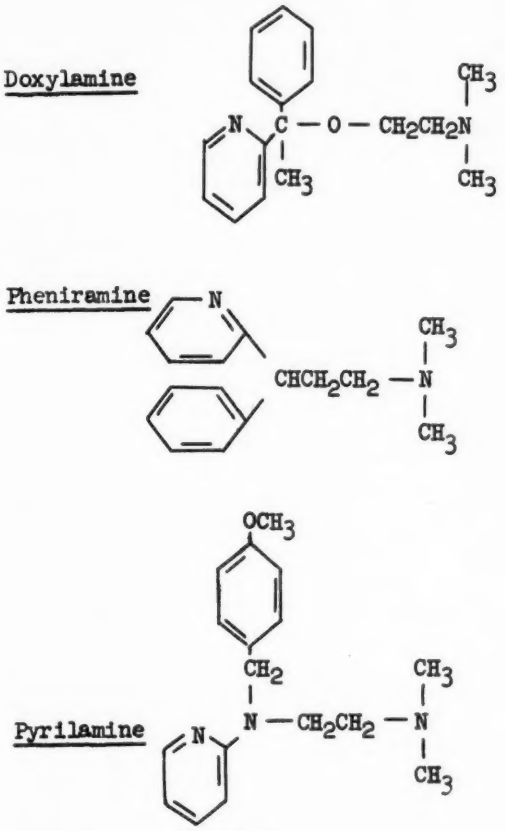

Fig. 1.

retained for assay. This procedure was repeated at two-hour intervals, using Simulated Intestinal Fluid, until the tablets or capsules were disintegrated.

The rates of release of the three preparations are shown in cumulative form in Figure 2.

Antihistamine A tablets did not disintegrate at a uniform rate. The range of disintegration time was from one to five hours. The ideal release rate curve for a repeat-action tablet of this type would have two

or more peaks at definite time intervals. The lack of such peaks is due to the fact that the release rate curve represents a composite average of twelve tablets and that the peaks for the individual tablets occur at different time periods.

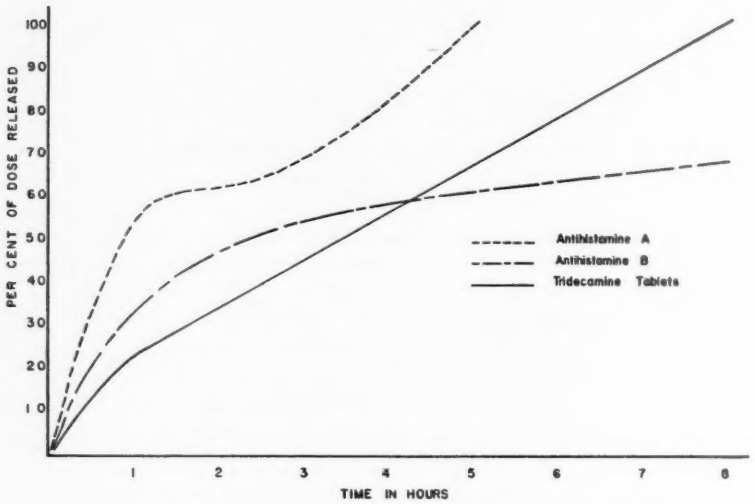

Fig. 2. *In vitro* release rates of three antihistaminic preparations.

TABLE I. DIAMETER OF WHEAL RESULTING FROM HISTAMINE DIPHOSPHATE* INJECTED INTRADERMALLY IN FLEXOR SURFACE OF FOREARM

Readings, Expressed in Centimeters, Were Made Fifteen Minutes After Each Injection

Subject	Control	Drug Administered	Time						
			2 Hours	4 Hours	6 Hours	8 Hours	10 Hours	12 Hours	14 Hours
GLC	1.5	None	2.2	2.0	2.1	1.8	2.0	1.6	2.2
PEH	1.2	None	1.6	1.9	2.0	2.2	2.0	2.0	2.2
EG	1.8	Tridecamine	1.2	1.3	1.2	1.2	1.1	1.5	1.4
FB	1.8	Tridecamine	1.7	1.2	1.4	1.2	1.5	1.8	1.4
LBD	2.5	Tridecamine	1.2	1.2	1.1	1.0	0.9	1.4	1.6
JK	1.4	Tridecamine	1.2	1.2	1.1	0.8	1.0	1.2	1.2
GW	1.8	Antihistamine A	1.5	1.2	1.1	1.7	1.6	1.6	1.8
CVG	1.6	Antihistamine A	1.5	1.5	1.2	1.2	1.5	1.8	1.9
CG	2.0	Antihistamine B	1.2	1.2	1.3	1.6	1.8	1.4	1.6
CF	1.8	Antihistamine B	1.5	1.5	1.8	1.6	1.8	1.5	1.8

*0.1 cc. of 1:10,000 dilution.

The release rate curve for Antihistamine B shows that only 70 per cent of the dose is released after eight hours. The diminishing slope of the curve indicates that some of the coated granules are very resistant to dissolution. Continuation of disintegration for an additional thirteen hours resulted in an additional 5 per cent dose recovery. These data are in general agreement with the report of Campbell and Theivagt[3] for this combination of sustained release medication. Royal[4] has also noted incom-

plete recovery of medications in *in vitro* disintegration studies with this physical form, and he observed great differences in rate of release between different brands.

The release curve for Tridecamine Dospan indicates a relatively sharp

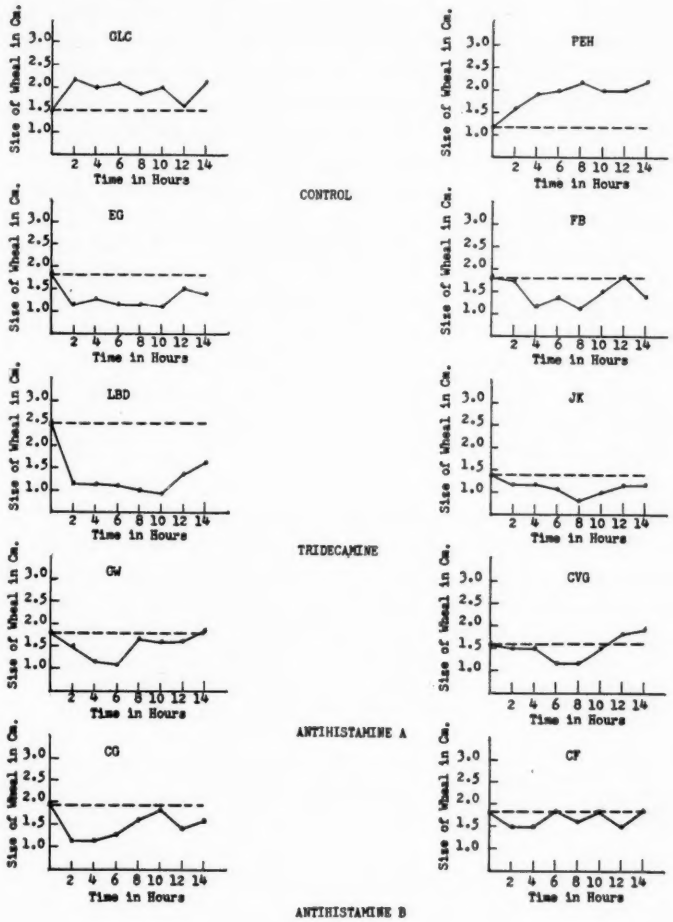

Fig. 3.

rise during the first hour, followed by a linear, even rate of release for the remaining seven hours. This even release rate is characteristic of the delaying matrix of the Tridecamine tablet. In all tests run, the total disintegration times for the individual tablets of Tridecamine demonstrated a remarkable uniformity with a spread of total disintegration times of less than thirty minutes between individual tablets.

In Vivo.—Response of the patient to intradermal histamine-neutralization tests was determined by the method described by Green.[5] Ten subjects received an intradermal injection in the forearm of 0.1 cc of a 1:10,000 aqueous solution of histamine diphosphate. The diameter of the resultant wheal was measured ten to fifteen minutes later. Each of four subjects received one Tridecamine Dospan tablet; two subjects each received one 6 mg Antihistamine A tablet; and two subjects each received one 12 mg Antihistamine B capsule. At two-hour intervals, over a course of fourteen hours, the injections were repeated as before.

The size of the wheal following intradermal injection of histamine is given in Table I for the two untreated control subjects and for each of the eight subjects receiving one of the three antihistaminic preparations tested. These data are illustrated in Figure 3. Reduction in the size of the wheal was greater and more prolonged following administration of Tridecamine Dospan than it was after administration of either Antihistamine A or Antihistamine B. One hundred per cent release of Tridecamine Dospan was obtained *in vitro* in eight hours, as evidenced by the curve in Figure 2. The duration of effect *in vivo* was twelve to fourteen hours, as shown by the curves in Figure 3. The difference can be accounted for by the fact that drug effect continues *in vivo* for a period of four to six hours following total release of the medication.

DISCUSSION

The duration of effect of Tridecamine Dospan, as evidenced by the intradermal histamine-neutralization test, is from twelve to fourteen hours. Constant suppression of wheal size indicates that the *in vivo* release is gradual, uniform and sustained. This correlates well with the *in vitro* release rate studies. These results also correlate with the prolonged duration of effect of Tridecamine Dospan in patients reported by two of the clinical investigators of this preparation.[2,6]

ACKNOWLEDGMENT

The authors wish to express their indebtedness to the members of the Analytical and Control Department of the Scientific Division, The Wm. S. Merrell Company, for their efforts and help in making this work possible.

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Submitted April 21, 1959

PRELIMINARY STUDY OF USE OF BUCCAL PROTEASE THERAPY IN BRONCHIAL ASTHMA

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THERE are many important factors that lead to the development of what we know as chronic "intrinsic" bronchial asthma. Unger[1] divides these into predisposing factors, constitutional, contributory factors, and exciting factors. Walzer[2] discusses race, age, sex, et cetera as general considerations in the etiology of asthma; predisposing factors such as heredity, presence of allergens, and finally the presence of acute, subacute, or chronic respiratory infections.

In this study we first had to accept the fact that in patients in the older age groups suffering from bronchial asthma, there not only were the components of "extrinsic" asthma caused by inhaled allergens, but also an intrinsic factor which Lowell states is a reactivity to non-specific factors in the absence of allergy. We are of the opinion that in the chronic bronchial asthmatic patient over forty years of age who has been under treatment for many years, but is still suffering from the disease, the infectious component can be severe. This will prevent the patient from reaching a plateau or "allergic balance" in which the attacks are much less frequent and more easily handled than at present.

Cooke[3] states that asthma may be caused by infection alone or in association with extrinsic factors, and he lists *Staphylococcus aureus* as one of the organisms most frequently encountered. There have been many workers such as Woodward,[4] Prissick,[5] Stiles and Chapman[6] who found the most common pathogen present in respiratory tract infections is *S. aureus*. Stiles and Chapman, in addition, found *S. aureus* to be present in 77 per cent of their asthma cases. Versteegh and Swiergeng[7] in 127 patients with chronic bronchitis, showed that 89 per cent of these manifested a clinical allergy. In addition to this, Zinnsser[8] stated that a hypersensitive state should be suspected in all sub-acute and chronic staphylococcic infections regardless of their location in the body. Baker[9] showed also that *S. aureus* was the most common aerobic pathogen encountered in cultures from the respiratory tract. Others such as streptococci, pneumococci, *H. influenzae*, and others, were seasonal.

It was our thought that after many years of therapy, consisting of hypo-sensitization and other supportive measures in some of our older chronic asthmatic patients, we were still not reaching nor destroying the infectious components. Many and varied courses of antibiotics both during and subsequent to respiratory infections did not entirely reduce the incidence or severity of the asthmatic attacks.

PATHOLOGY

In any inflammatory process, the early stage of local vasodilitation, increased capillary permeability, and leukocytic migration in the damaged area is followed by a swelling of the capillary endothelium, gradual slowing down of the circulation, formation of highly polymerized particles of microthrombi in the process of fibrin clotting, and also clumping of the leukocytes. Thus, that which began as a mechanism which mobilized the *offensive* forces of the body evolves finally in a *defensive* "walling off" of the injured area as stasis develops. In this area, changes seen under anoxic conditions occur such as vigorous glycolysis, lactic acid accumulation, increased carbon dioxide tension, decreased oxygen tension, and potassium concentration. All of this contributes to the abnormal metabolism existing in the involved tissue. The stasis is further intensified by impairment of the connective tissue permeability through fibrin formation, edema, and thickening of the exudate, as well as the resultant release of desoxyribonucleoprotein from cellular debris. This resultant localization removes the causative factor from the rest of the body by walling it off, but in essence serves to isolate the necrotic process from the rest of the body. This interferes with the normal reparative processes. One of the results of this process is the interference with access to this area of most exogenous and endogenous therapeutic agents.

The body's attempt to reverse this inflammatory situation is affected by the proteolytic enzyme system. A fibrinolytic system is established with kinase activation of plasminogen to form plasmin. The resultant dissolution fibrin thins the exudate and increases the tissue and capillary permeability. Thus the primary reactions of inflammation are re-established, and the increased blood flow, leukocyte migration, plus the capillary permeability increase, allows the body to destroy or cause to revert to normal, the inflammatory process.

It was our thought that, since the antibiotics alone would not destroy the infectious processes and reach the walled-off areas of infection and the necrotic material within the lung tissue itself in those with chronic "intrinsic" asthma (or mixed "extrinsic" and "intrinsic"), a drug which would increase the anti-inflammatory activity in the area and accelerate the plasminogen-plasmin system would allow the body to destroy these areas of infection. Also, it would allow exogenous and endogenous processes to work more successfully.

METHOD

We decided to evaluate the use of buccal Varidase for this type of therapy. If we had marked subjective improvement to a demonstratable degree we would then proceed with a "double blind" study. In other words, if the Varidase, with or without a broad-spectrum antibiotic in proper dosage, would reverse the pathology in the lungs described above, we could then determine whether a full-scale study was warranted.

TABLE I. PATIENTS SELECTED

Age Groups			Severity of Disease			Duration of Illness		
35-42	43-50	51-72	Severe	Moderate	Mild	5 Years or Less	6 to 10 Years	More Than 10 Years
3	11	9	15	8	0	2	7	14

The additional patients represented were added after this preliminary paper was submitted.

These results are of the preliminary procedure:

There were twelve patients selected from Mt. Sinai Hospital adult allergy clinic and our private practice. These patients have been under care for five to twenty-two years. They all are receiving hypo-sensitization as well as other medications, such as Tedral, Aminophyllin tablets or suppositories, iodides, various cough medications, antihistimines, et

TABLE II. RESULTS

Onset of Relief		Duration of Relief			Amount of Relief		
Less Than 3 Weeks	3 Weeks To 6 Weeks	12 Weeks or More	6-12 Weeks	Less Than 6 Weeks	Complete	Partial	No
18	3	10	8	3	14	5	2

The additional patients represented were added after this preliminary paper was submitted.

cetera. No part of their therapy was changed except for the addition of buccal Varidase alone or in combination with an antibiotic as described below. All of these patients without exception have had one or more courses of antibiotics previously without any marked improvement.

Our impressions are that every patient who started on buccal Varidase began to show improvement. At first, the patients began to expectorate a good deal of "coughed up" necrotic material which, when placed upon culture showed predominantly *S. aureus* as well as other associative bacteria. The incidence of attacks, even during the seasons in which the patients had previous serious difficulties, were lessened. On the whole, the attacks were less severe, and a great deal more easily controlled with the usual drugs the patient had been accustomed to taking. The patients who did best were those who received a course of buccal Varidase for one week, Achromycin V (1 gm daily), plus Varidase for two more weeks, and then another week on Varidase alone. Toward the end of this four-week period, the patients on this routine showed some fairly remarkable results.

REPORT OF CASES

D. B., a colored woman, aged forty-two, had taken an average of four Tedral tablets per day and an Aminophyllin suppository at bedtime for the previous eighteen months. She had recurrent respiratory infections which had been treated with many various antibiotics, sulfa, penicillin, and so forth. On an average of every ten days she had received epinephrine or intravenous aminophyllin. By the end of the second

week of therapy, she stated that she had taken only two Tedral tablets within the last five days, and no suppositories, with no visits to the emergency room, and had "not breathed as easily for years." By the end of the four weeks this patient was in better health and had more freedom from attacks than she had in the previous five years of attending the allergy clinic. This situation continued until the present (which is over three months since the cessation of that therapy).

L. P., a white female patient seen in our private office, had a long history of intrinsic asthma. She received the Varidase and achromycin, as above, and then all therapy stopped. Her condition improved more markedly than at any time in the past, and she is still progressing more satisfactorily than at any time in our seven years' experience with this patient.

CONCLUSION

We feel that the reason these patients improved was the fact that the Varidase increased the body's ability to break down the walled-off areas and helped to reverse the chronic inflammatory process to a point where the body could use its own mechanisms for destroying the foci of infection. In addition, the achromycin was also able to reach these more permeable foci. We do not claim by any means that this is the final answer for chronic "intrinsic" asthma, but we certainly are encouraged enough to go on with a more extensive study.

Further study will utilize cultures before and after the use of Varidase, specific sensitivity tests for determining which antibiotic will be most effective, respiratory studies and evaluation, and, of course, the use of placebos. We hope to show that intrinsic asthmatic patients can be markedly improved by destroying the infectious component. The patients will be divided into four groups in a double blind study. One group will receive only an antibiotic, one only buccal Varidase, the third buccal Varidase plus the antibiotic, and the fourth only placebos. We hope to have these results sometime in the near future.

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Submitted January 21, 1959
Resubmitted April 13, 1959

DEXAMETHASONE IN CHILDHOOD ASTHMA

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THE JEWISH National Home for Asthmatic Children (JNHAC) in Denver provides facilities[1] for the intensive diagnostic investigation and long-term therapeutic management of chronic intractable asthmatic children of both sexes, six to sixteen years of age. The Home accommodates 150 children. There are seventy to eighty new admissions each year and the average length of stay is eighteen to twenty-four months.

A progressively increasing number of the children admitted in recent years gave a history of prolonged therapy with anti-inflammatory steroids, and the majority of them were still on one of these drugs at the time of admission.[1,2] Table I summarizes the data for the two year period July 1, 1957 to June 30, 1959.

TABLE I. INCIDENCE OF ANTI-INFLAMMATORY STEROID THERAPY AMONG NEW PATIENTS ADMITTED TO THE JNHAC

	7-1-57 to 6-30-58		7-1-58 to 6-30-59	
	Number	Per Cent	Number	Per Cent
Total admissions	88	—	63	—
Previous therapy	65	75	61	97
Maintenance on admission	44	50	32*	51
No previous therapy	23	25	2	3

*Three additional cases were on AIS until 5-21 days preceding admission.

The steroids can be gradually withdrawn from a large percentage of these children within the first two or three months of residence.[2] There is, however, an irreducible minimum of children who require steroid therapy for prolonged periods of time and, in certain cases, for the duration of their stay. The compound most generally employed has been prednisone.* A daily dose of 2.5 to 10 mg. of prednisone has been found to be an effective maintenance dose in controlling all but the most severe asthmatics and allowing them to pursue the normal activities for their age. At this dosage range none of the well known undesirable effects of induced hypercortisonism have been noted. The age or size of the child did not seem to play any significant role in determining the amount of prednisone required for adequate maintenance clinical control of asthma after initial control with the larger doses usually required for a short period.[3] The new 9-alpha-

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From the Jewish National Home for Asthmatic Children, and Children's Asthmatic Research Institute and Hospital in Denver.

*Generously supplied as Meticorten by Schering Corporation.

fluoro-16-alpha-methyl derivative of prednisolone, dexamethasone, has been reported by its manufacturers to have at least six times the anti-inflammatory activity of prednisone or prednisolone and to be exceptionally free of the side effects associated with the administration of cortisone and its various analogues. This has been confirmed by some studies abroad.[4]

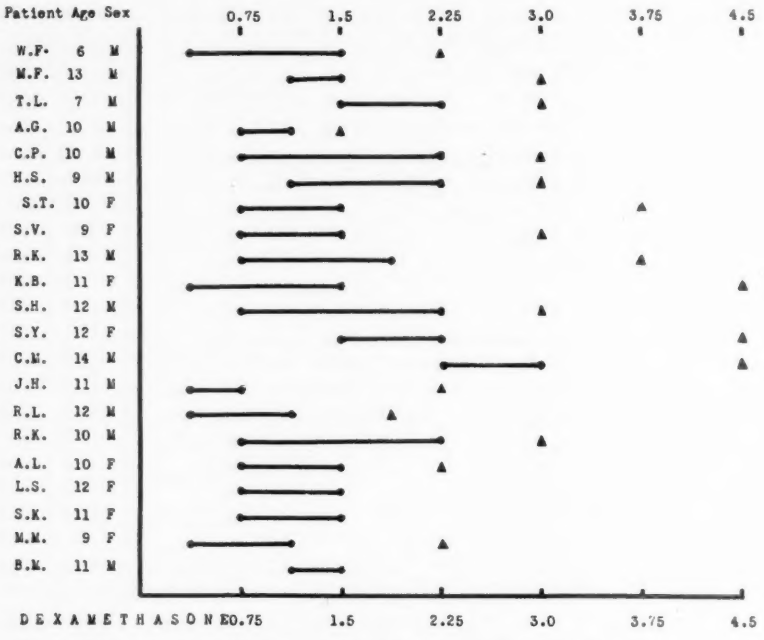

Fig.1. Daily maintenance dosage range (●——●) of dexamethasone and maximum 24-hour requirement for severe attacks (▲) of asthma among 21 asthmatic children at the J.N.H.A.C.

Fig. 1.

PRESENT STUDIES

Dexamethasone* was prescribed for twenty-one children with severe intractable bronchial asthma, during a period of six months, from November, 1958, to April, 1959. In addition, one patient, whose asthma was well under control, and who developed rheumatic pericarditis during that same period, was also given a course of this newer steroid.

The duration of therapy with dexamethasone ranged from twenty-three to eighty-four days, with a median of forty-seven days. All but two of the children were on prednisone prior to the introduction of dexamethasone, and prednisone was again resumed after the trial period on dexamethasone. The two patients who were not on steroid therapy immediately preceding

*Generously supplied as Deronil by Schering Corp., Bloomfield, N. J.

the course of dexamethasone had received prednisone previously, up to twelve and fifteen days, respectively, prior to the introduction of dexamethasone. In these two cases dexamethasone was given for an acute exacerbation of asthma, not controllable by other means. After control

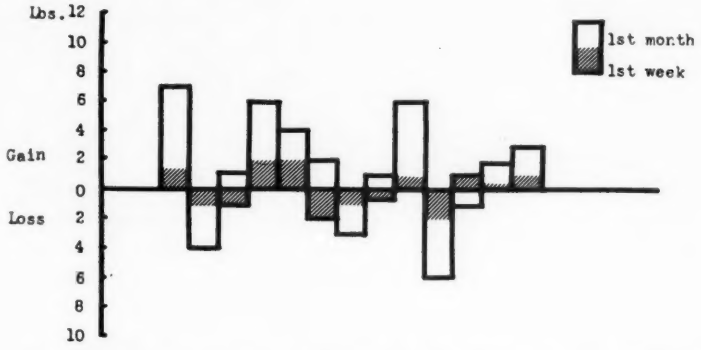

Fig. 2. Weight changes among thirteen asthmatic children on dexamethasone 0.75-1.5 mg daily.

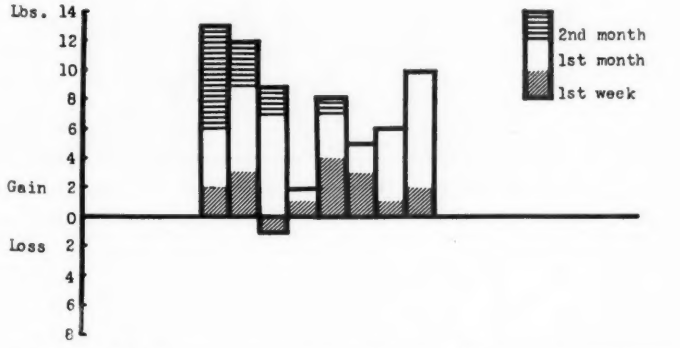

Fig. 3. Weight changes among eight asthmatic children on dexamethasone in excess of 1.5 mg daily.

was achieved, the steroid was progressively discontinued without any further need for the drug.

Figure 1 lists by age and sex twenty-one patients to whom dexamethasone had been given, as well as their daily maintenance and maximum twenty-four hour dose requirement. Thirteen children were maintained reasonably free of asthma on a dosage of 0.375 to 1.5 mg. (½-2 tablets) daily, while the remaining eight required more than 1.5 mg. daily. There was only one patient, a fourteen year old boy (C.M.), who experienced severe exacerbation of symptoms following any attempt to reduce dexamethasone below 2.25 (0.75 mg. t.i.d.) mg. daily.

The dosage level for adequate control of asthma was determined, initially, by substituting 0.75 mg. of dexamethasone for each 5 mg. of prednisone. A gradual dosage reduction within a period of five to seven days

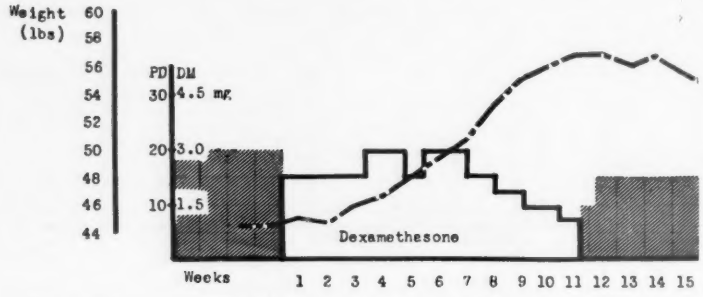

Fig. 4. T.L., seven-year-old boy, has been on anti-inflammatory steroids since the age of two years.

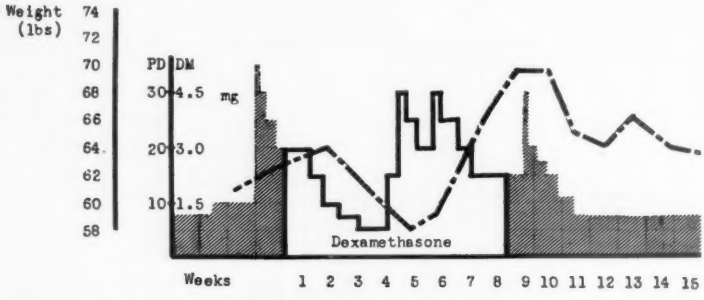

Fig. 5. H.S., nine-year-old boy, was asthmatic since the age of five. He had been on anti-inflammatory steroids for two and one-half years prior to admission to J.N.H.A.C.

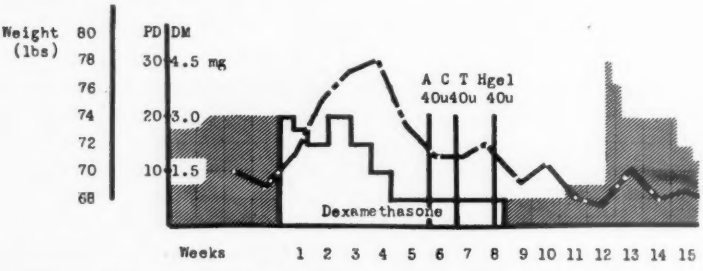

Fig. 6. R.K., ten-year-old boy, has a history of asthma since infancy. He has been on continuous anti-inflammatory steroid therapy for the past two years and intermittent therapy before.

was attempted whenever the clinical condition of the patient permitted and the minimum daily dose was thus established.

An amount of dexamethasone considerably greater than the maintenance

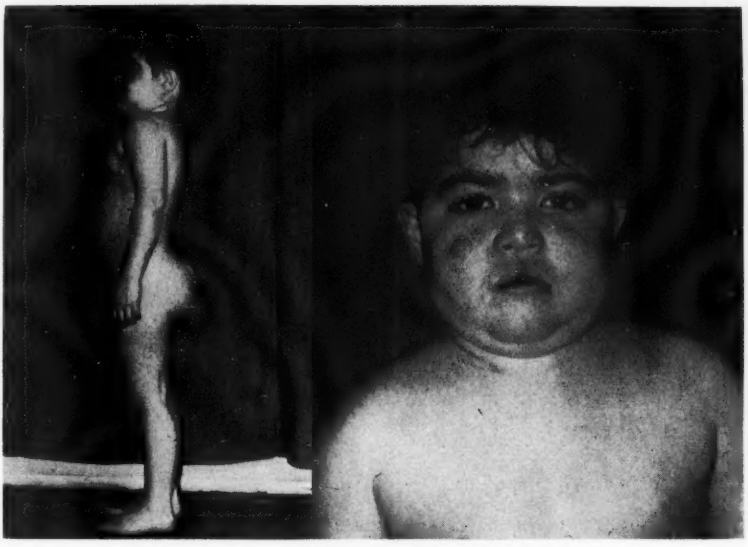

Fig. 7. T. L. Cushingoid appearance is apparent.

dose frequently had to be given for twenty-four to forty-eight hours when exacerbations of asthma occurred. This maximum dose given is also indicated in Figure 1, and in only three cases was there no need for increasing the dose over the maintenance requirement (L.S., S.K., B.M.). In general, 0.75 mg. of dexamethasone were equivalent to 5 mg. prednisone in anti-asthmatic effect.

Side effects were not observed in the group that received an average daily dosage of 1.5 mg. of dexamethasone, or less. There was no pronounced weight change among this group of thirteen children, of whom six gained from one to seven pounds during a period of one month (Fig. 2), three others lost three to six pounds, and the remaining four showed only minimal fluctuation in weight. No significant changes, at the end of the second month, were observed.

The pronounced weight increase observed in the group that received an average maintenance dosage exceeding 1.5 mg. daily was in marked contrast to the above. All eight children gained weight, the increase ranging from two to ten pounds in one month to thirteen pounds at the end of the second month on dexamethasone. Only a part of this weight increase could be attributed to an amelioration of symptoms with increased appetite and well being, because all of these children had previously been on prednisone, which adequately controlled their asthma. This increase in weight was, as a rule, associated with rapid development of moon face, buffalo hump, hirsutism and, in some cases, acne and striae. Interestingly, the rate of weight gain persisted and was not reversed until often two to three weeks after dexamethasone had been markedly reduced or discontinued.

Figures 4 to 6 depict, graphically[5] the cases of three patients who showed the most marked gain in weight. Figure 4 shows the delayed weight gain in case T.L. mentioned above. The general cushingoid appearance of this

Fig. 8. Localized swelling of the soft tissues over the zygomatic arch.

Fig. 9. Moon-face and punctuate skin lesions after two weeks on dexamethasone.

child is well shown in Figure 7. Figure 5 (H.S.), reveals the marked loss of weight accompanying rapid reduction in dosage of dexamethasone (first to fourth week). There was simultaneously a severe recurrence of asthma, and a subsequent increase in dosage for three weeks was followed by a marked weight gain persisting for several weeks after a second reduction in

dosage. An extremely rapid weight gain occurred in a ten-year-old boy (R.K.), as illustrated by Figure 6. At the height of the weight gain, this boy developed a painful localized swelling of the soft tissues over the

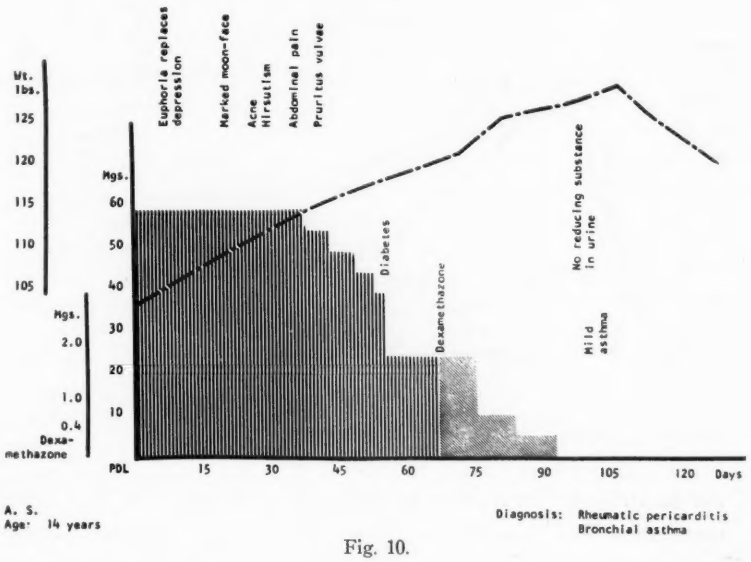

Fig. 10.

zygomatic arch (Fig. 8). This subsided, and his weight returned to previous levels, following a rapid reduction in dexamethasone. It is noteworthy that a course of prednisone several weeks later, in analagous amounts, did not affect the weight in the fashion dexamethasone did.

Figure 9, taken from color slides, illustrates the typical moon faces and, less satisfactorily, the punctate, pale lesions on the hyperemic face of two girls who had been on dexamethasone 1.5 to 2.25 mg. daily, for a period of less than two weeks. These lesions also disappeared after dexamethasone was discontinued and prednisone was resumed.

Figure 10 depicts the course of a fourteen year old girl who developed rheumatic pericarditis one month after her admission, and was treated with amounts of prednisone much larger than those usually employed for the management of asthma. The incidence of side effects is shown on the graph. No change was observed when dexamethasone was substituted for prednisone, and the patient continued to gain weight until one week after the discontinuance of steroid therapy. The glucose tolerance curves (Fig. 11) are also characteristic in that the patient continued to exhibit typical diabetic curves (as well as clinical diabetes), in spite of a reduction in dosage of prednisone or switch to dexamethasone. All evidence of diabetes disappeared one week after corticosteroids were discontinued.

SUMMARY

Dexamethasone was given to twenty-one children with intractable asthma and one child with rheumatic pericarditis at the Jewish National Home for Asthmatic Children. The anti-inflammatory and anti-asthmatic effect of

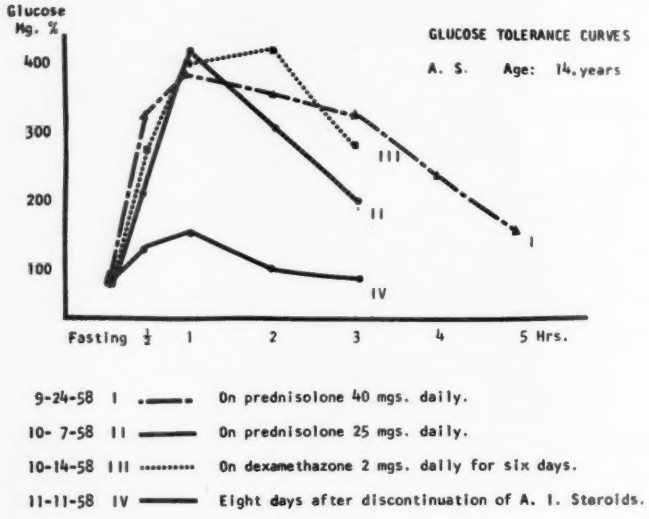

Fig. 11.

this newest steroid were found comparable to that of prednisone, 0.75 mg. of dexamethasone being equivalent to 5 mg. of prednisone.

In the dosage range below 1.5 mg. of dexamethasone daily, no side effects were noted. With higher dosages various signs of hypercortisonism were noted, prominent among which was a considerable gain in weight. This was corrected by a reduction in, or discontinuance of, dexamethasone.

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DEXAMETHASONE IN DERMATOLOGIC THERAPY

Study of Case Reports

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DEXAMETHASONE* is the latest cortisone analogue to be made available for therapeutic use. The claim made for this steroid is that it is more potent than its predecessors, being four to six times more active milligram for milligram than triamcinolone and 6-methylprednisolone, six to eight times more potent than prednisone or prednisolone, twenty-five to thirty times more active than hydrocortisone and thirty-five times more potent than cortisone.

It is stated that one 0.75 mg of Dexamethasone will usually replace one 4 mg tablet of methylprednisolone or triamcinolone, one 5 mg tablet of prednisolone or prednisone, one 20 mg tablet of hydrocortisone, or one 25 mg tablet of cortisone. The anti-inflammatory effect, on the basis of weight, therefore, makes the drug more potent than any previously known glucocorticoid. The mineralocorticoid activity is said to be negligible and as a result electrolytic inbalance is usually not an important problem in ordinary dosages.

PROCEDURE

A study was undertaken to determine the effectiveness of Dexamethasone in various dermatologic diseases. Dexamethasone was orally administered to patients suffering from contact dermatitis, atopic dermatitis, urticaria, erythema multiforme, intertrigo, and scleroderma.

The patients are tabulated in Table I. The diagnoses are listed along with previous therapy, concurrent therapy, dosages of dexamethasone, and the results of therapy. Some patients had received other steroid therapy previously but this had been discontinued by the time dexamethasone had been started. Concurrent therapy, where given, consisted of small doses of grenz ray therapy, and/or the antihistamine, dimethane. Antibiotics, either chloramphenicol or erythromycin, were given for secondary infection.

The degree of improvement was listed as "excellent," "satisfactory," or "no improvement." The terms "excellent" or "satisfactory" are arbitrary ones based upon the time noted for healing and subjective relief. If the dermatitis was clearing rapidly and marked clinical improvement was noted within three days after the start of therapy, the designation "excellent" was used. If the dermatitis cleared more slowly and the time interval to secure clinical improvement was longer, the term "satisfactory" was used.

*Dexamethasone was supplied as Decadron in 0.5 mg tablets by Merck, Sharp & Dohme Research Laboratories—West Point, Penna.

TABLE I. RESULTS OF DEXAMETHASONE THERAPY

Patient	Sex	Age	Diagnosis and Duration of Disease	Previous Steroid Therapy				Dexamethasone Therapy				Other Concurrent Therapy	Degree of Improvement on Dexamethasone
				Type	Duration	Interval Before Dexamethasone Administered	Other Previous Therapy	Initial Dose	Duration of Initial Dose	Average Maintenance Dose	Total Duration of Dose		
1	M	35	Contact dermatitis 6 months Superimposed on widespread psoriasis—due to topical medication.	Triamcinolone	2 weeks	2 weeks	Antihistamines—benadryl chlortrimeton 3 weeks	1.5 mgs daily	2 weeks	.5 mg daily	4 weeks	Grenz ray	Excellent
2	M	72	Contact dermatitis 4 weeks Wrists and forearms—due to topical medication.	None	None	None	None	2.0 mgs daily	4 days	None	4 days	Grenz ray	Excellent
3	M	70	Contact dermatitis 5 days Elbows Etiology undetermined. Similar attack 2 months previously.	None	None	None	None	1.5 mgs daily	7 days	.5 mg daily	13 days	Grenz ray	Satisfactory
4	M	68	Contact dermatitis 2 months Scalp—due to proprietary scalp lotion.	ACTH Triamcinolone	1 week	1 week	Topical lotion applications 4 weeks	2.0 mgs daily	8 days	.5 mg daily	12 days	Grenz ray	Excellent
5	F	22	Contact dermatitis 2 weeks Hands—due to a detergent.	None	None	None	None	1.5 mgs daily	6 days	.5 mg daily	9 days	Grenz ray	Excellent
6	F	25	Contact dermatitis 1 month Hands—due to a detergent.	None	None	None	None	3.0 mgs daily	7 days	.5 mg daily	13 days	Grenz ray	Excellent
7	F	36	Contact dermatitis 6 months Hands—due to citrus fruits	None	None	None	Proprietary ointments. 3 months	2.0 mgs daily	9 days	.5 mg daily	14 days	Grenz ray	Excellent
8	F	23	Contact dermatitis 1 year Hands—due to certain raw fruits and vegetables.	Topical hydrocortisone creams	Off and on for six months	2 months	Silicone ointments (intermittently)	2.0 mgs daily	7 days	.5 mg daily	14 days	Grenz ray	Satisfactory
9	F	42	Contact dermatitis 7 months Hands—due to certain raw fruits and vegetables.	None	None	None	Hand creams (intermittently)	2.0 mgs daily	7 days	.5 mg daily	14 days	Grenz ray	Satisfactory

10	F	24	Contact dermatitis 1 week Eyes—due to nail lacquer.	None	None	None	Proprietary ointments 5 days	2.0 mgs daily	5 days	.5 mg daily	7 days	Grenz ray	Satisfactory
11	M	51	Atopic dermatitis 25 years Neck, elbows, legs	None	None	None	Topical lotion antihistamines	2.0 mgs daily	7 days	1.0 mg daily	11 days	Ilotycin for secondary infection	Satisfactory
12	F	48	Atopic dermatitis 30 years Neck, elbows, arms, legs, chest	Triamcinolone ACTH	Intermittent	3 months	Topical lotion antihistamines	2.0 mgs daily	9 days	.5 mg daily	14 days	None	Excellent
13	F	22	Atopic dermatitis 22 years Neck, elbows, legs	ACTH prednisone	Intermittent	6 months	Topical lotion antihistamines	1.5 mgs daily	5 days	.5 mg daily	8 days	None	Satisfactory
14	F	18	Atopic dermatitis 18 years Neck, elbows, arms, legs	ACTH prednisone	Intermittent	3 months	Topical lotion antihistamines	2.0 mgs daily	6 days	.5 mg daily	10 days	None	Satisfactory
15	M	46	Chronic urticaria 6 years (cause unknown)	Prednisone	2 months	3 months	Topical lotion antihistamines intermittently	1.5 mgs	3 days	.5 mg daily	5 days	Antihistamine dimetane	Satisfactory
16	F	32	Acute urticaria 1 week Drug allergy	None	None	None	Topical lotion antihistamines theruhistin. phenergan 5 days	1.5 mgs	7 days	None	1 week	None	Excellent
17	M	21	Acute urticaria 3 days Drug allergy	None	None	None	Topical lotion antihistamines chlortrimeton 3 days	2.0 mg	7 days	None	1 week	None	Excellent
18	F	42	Acute urticaria 2 days Drug allergy	None	None	None	Topical cream antihistamines dimetane 1 day	2.0 mg	7 days	.5 mg daily	10 days	None	Excellent

TABLE I. RESULTS OF DEXAMETHASONE THERAPY (CONT'D.)

Patient	Sex	Age	Diagnosis and Duration of Disease	Previous Steroid Therapy				Dexamethasone Therapy				Other Concurrent Therapy	Degree of Improvement on Dexamethasone
				Type	Duration	Interval Before Dexamethasone Administered	Other Previous Therapy	Initial Dose	Duration of Initial Dose	Average Maintenance Dose	Total Duration of Dose		
19	M	41	Erythema multiforme 5 days Infectious etiology	None	None	None	Topical cream antihistamines chlortrimeton—3 days	2.0 mgs	7 days	.5 mg daily	10 days	Chloromycetin for infection antihistamine dimetane	Excellent
20	F	18	Erythema multiforme 1 week Drug allergy	None	None	None	Topical lotion antihistamine polaramine 5 days	2.0 mg	7 days	.5 mg daily	10 days	Antihistamine dimetane	Excellent
21	F	73	Intertrigo 3 weeks Mammary genito-crural regions	None	None	None	Topical cream antihistamine benadryl 2 weeks	2.0 mg	10 days	.5 mg daily	14 days	Antihistamine dimetane Grenz ray	Satisfactory
22	M	25	Intertrigo 1 week Genito-crural, axillary regions	None	None	None	Topical cream antihistamines chlortrimeton 1 week	1.5 mgs	8 days	.5 mg daily	14 days	Antihistamine dimetane	Satisfactory
23	F	67	Intertrigo 1 month Axillary, mammary, genito-crural regions	Triamcinolone	1 week	2 weeks	Topical cream antihistamine pyribenzamine 2 weeks	1.5 mgs	10 days	None	14 days	Antihistamine dimetane	Satisfactory
24	F	47	Intertrigo 2 months Genito-crural region	ACTH prednisolone	3 weeks	3 weeks	Topical lotion antihistamines phenergan chlortrimeton 1 month	1.5 mgs	8 days	.5 mg daily	14 days	None	Satisfactory
25	F	51	Scleroderma 1 year Ankles	ACTH prednisolone	3 months	2 months	Physical therapy	2.0 mgs	1 month	2.0 mg daily	1 month	Physical therapy	None

RESULTS

The result of therapy may be noted on Table I. We consider Dexamethasone to be a very effective therapeutic agent. It proved to be satisfactory in some cases where other steroids and ACTH had failed. Our impression was that, milligram for milligram, it is the most potent steroid available. Kohn and Grater[1] in an evaluation of this drug in various allergic disorders confirm this finding.

TABLE II. RESULTS OF TOPICAL DEXAMETHASONE THERAPY

Disorder	Number of Patients	Results
Second degree burns	4	excellent
Contact dermatitis	2	excellent
Atopic dermatitis	2	excellent
Intertrigo	2	excellent

We did not note any undesirable side effects. Our series of cases were treated mostly on a short term basis. Kohn and Grater[1] in a larger series of allergic disorders (240 cases), with some patients treated on a long term basis, noted no serious side effects. They did report that the outstanding side effects seen were increased appetite with weight gain and increased nervousness. Kanof and Blau[2] treated forty-seven dermatologic cases and reported increased appetite and weight gain as the outstanding side effect, jittery symptoms were of lesser importance. Our patients were already nervous and emotionally upset by their skin disorders and such symptoms could not be properly evaluated. Two complaints referrable to gastrointestinal discomfort were elicited. About one-third of the patients reported an increased sense of well being. Hematologic and urine studies showed no abnormalities. No evidence of adrenal insufficiency was seen after discontinuing therapy. According to Friedman,[3] when short term therapy has ceased, the effects of dexamethasone are no longer evident after a week. This was determined by hydroxy-steroid blood levels and corticotropin responses.

DISCUSSION

Dexamethasone was orally administered to twenty-five dermatologic patients. They were treated for contact dermatitis, atopic dermatitis, urticaria, erythema multiforme, intertrigo, and scleroderma. The response was excellent in twelve patients and satisfactory in twelve. One case of scleroderma showed no improvement. Scleroderma does not respond well to steroids.[4] The effective dose of dexamethasone varied from 1.5 to 3.0 milligrams. The maintenance dose varied from 0.5 to 1 milligram. These doses are somewhat lower than those reported by other investigators. (Since the availability of 0.75 milligram tablets we have used higher doses to more quickly attain a therapeutic effect—using 2.25 to 4.5 milligrams and giving a maintenance dosage of 0.75 to 1.50 milligrams.)

TOPICAL THERAPY

Dexamethasone was supplied as the phosphate in 0.1 per cent concentration in a cream base to determine its effects topically. The results are shown in Table II.

The dexamethasone was applied locally to second degree burns, lesions of contact dermatitis, atopic dermatitis, and intertrigo. Therapeutic results were excellent in the ten treated cases. Response was rapid. None of the patients had received previous steroid therapy either systemically or locally. In view of the small amount of material available it was not possible to treat more patients nor to compare dexamethasone topically with other steroids.

CONCLUSIONS

Dexamethasone, when orally administered, was found to be an effective anti-inflammatory agent in the treatment of various dermatologic disorders such as contact dermatitis, atopic dermatitis, erythema multiforme, urticaria, and intertrigo. It was ineffective in one case of scleroderma. No undesirable serious side effects were noticed.

Dexamethasone was an effective anti-inflammatory agent when used topically in second degree burns and lesions of contact dermatitis, atopic dermatitis, and intertrigo.

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ACKNOWLEDGMENT

The author wishes to express his appreciation to his office assistants, Wilma J. Hickerson and Colleen A. Winker, for their help in preparing this manuscript.

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Submitted March 23, 1959
Resubmitted August 27, 1959

BASIC RESEARCH

I think that important basic research is characterized by three features, some of which may seem self-evident, while others may seem ridiculous to you, but we shall analyze them. These three features are: that it must be *true,* it must be *generalizable,* and it must be *surprising.* It is also important that all three characteristics be present at the same time, and that they be present at the time the discovery is made.—HANS SELYE, What Is Basic Research? *Metabolism,* VII:4, 392 (July) 1958.

CONSTITUTIONAL REACTION FOLLOWING BUCCAL TRYPSIN

A Case Report

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The following case is reported because a review of the current literature failed to reveal any previous report of either urticaria or an anaphylactoid reaction from buccal trypsin. Urticaria following administration of such fibrinolytic agents as buccal varidase,[1] streptokinase, and streptodornase[2] has been reported. Anaphylactoid reactions from intravenous and intramuscular trypsin had been reported and will be discussed at the conclusion of the case report. However, the presence in this patient of a positive delayed reaction to intradermal testing with trypsin, as well as a delayed positive passive transfer test, was felt to be worthy of note.

CASE REPORT

Mrs. J.S., a thirty-one-year-old blind woman, was first seen at the Allergy Clinic at the Methodist Hospital in April, 1958. She presented a history of perennial nasal plugging of four years' duration. She was worse indoors and at night and did better while at work. Cigarette smoke, house dust, cosmetics, and the ragweed pollen season were known to be clinically significant. There were no known food allergens. The patient never has asthma, and antihistamines gave her relief.

Past history revealed that this patient had become blind at the age of four following pertussis. Since that time she has had cataract surgery twice and has suffered a great deal from painful granulations on the bulbar conjunctiva. Her health otherwise has been quite good. She has had one pregnancy, and now has a boy six years of age. She is employed as a typist in the record department of the hospital. Family history is negative for allergic disease.

Physical examination revealed a well developed, well nourished white woman, approximately thirty years old, who did not appear to be acutely ill. The examination was within normal limits, with the exception of the eyes and the nose. The bulbar conjunctiva was markedly fibrotic so that landmarks could not be differentiated. The nasal mucosa was pale, boggy and swollen, with a typical bluish color.

Skin tests were positive to house dust, mohair, orris root, tobacco smoke, flaxseed, karaya gum, ragweed, alternaria, monilia, penicillium, and stemphyllium. Many household allergens and also grass pollens, molds, and tree pollens were negative. Foods including pork and beef were negative. Laboratory data revealed normal hemoglobin, white blood count, differential (6 per cent eosinophils) and urinalysis. A nasal smear was negative for eosinophils.

This patient was treated with a mixture of house dust, molds, ragweed and tobacco smoke. Under this regime she improved considerably and was quite happy with the results of therapy. She required only an occasional antihistamine tablet for symptomatic relief.

In early August of 1958, this patient developed a chronic urticaria which we were unable to explain. Repeated physical examinations, laboratory examinations includ-

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ing white blood counts and differentials, stools for ova and parasites, chest x-ray, sedimentation rate, and C reactive protein studies were all within normal limits. She ceased all medication except an occasional antihistaminic agent, and was placed on an allergy trial diet to remove common food offenders. Her hives persisted. After six weeks, her case was reviewed. At this time it was found that she had been taking a Vitamin A capsule containing 50,000 units of Vitamin A twice daily for the granulations on her conjunctiva. She did not consider this a drug and had kept taking it. Shortly after discontinuing these capsules her hives disappeared.

Two weeks later she consulted an oculist because of the painful conjunctival granulations. She was given ½ cc Parenzyme® intramuscularly. She was also placed on buccal tablets of Parenzyme-B® twice daily. Twenty-four hours later she developed a generalized urticaria. At this time she started to take the buccal Parenzyme-B® tablets. She took one in the morning and one again in the afternoon. Shortly after the second buccal Parenzyme-B® tablet had dissolved, her urticaria became extremely severe and generalized so that her entire body was covered with giant wheals. She developed severe asthma, became stuporous and went into shock. Fortunately this occurred while the patient was at work in the hospital. She was given .2 cc 1-200 susphrine subcutaneously with marked relief of her symptoms. Over a period of several days her hives gradually disappeared.

Correspondence with the National Drug Company revealed that Parenzyme-B® tablets contain: (1) magnesium sterate powder, (2) carbowax, (3) corn starch, (4) potato starch, (5) lactose, (6) granulated sugar, and (7) trypsin. The company was kind enough to send us a sample of each ingredient for clinical testing.

The patient and three controls were scratch tested with all ingredients, and all tests were negative. The powdered trypsin was then dissolved in buffered saline. Intradermal testing was started with a 1-1,000,000,000 dilution, and with negative tests each subsequent test was increased ten-fold in strength. At 1-10,000 dilution of trypsin, the three controls and the patient all gave an immediate positive reaction. With this information it was felt that the results of the experiment were inconclusive and further investigation was to be discontinued. However, about thirty-six hours following the testing, the patient developed a severe pruritic angio-edema at the sites of the intradermal testing which persisted for over forty-eight hours. This could indeed be described as similar to a severe edematous delayed type of tuberculin reaction. A check of the controls revealed no such reactions, and the testing sites had entirely cleared.

With this new evidence at hand, blood was obtained from the patient for passive transfer. As expected, house dust, ragweed, and tobacco smoke transferred quite well. Passive transfer sites were challenged with 1-10,000 trypsin. An immediate wheal developed in fifteen minutes as it had previously done on all controls as well as on the patient. Forty-eight hours later, these sites revealed the same delayed type reaction and the control arm was negative.

DISCUSSION

Slepian[3] discussed skin testing with trypsin. He skin tested and did passive transfer studies on patients who had constitutional reactions from intravenous trypsin, as well as controls, and was unable to demonstrate antibodies against trypsin. He felt that what reactions did occur were on the basis of proteolytic enzymes and not antibodies. He also called attention to the similarity between injected snake venom and trypsin. Both release proteolytic enzymes and histamine. However, Wells and others[4] were unable to modify the lethal action of trypsin in the guinea pig or dog with benadryl.

Ratner and others[5] discussed the evolution of the delayed type reaction to the immediate wheal type of reaction. They felt that in the development of hypersensitivity, the delayed tuberculin type reaction was first developed, only to be replaced in time by the immediate wheal type of response. The presence of a positive delayed passive transfer test in our patient is difficult to explain. It is difficult to be certain that the serum used in the passive transfer test contained no lysed white cells. This might explain how we obtained our positive test on passive transfer. If not, we indeed have a unique antibody. We feel that in this patient it is quite possible that we are seeing a patient in the early state of her hypersensitivity and thus have found a positive delayed reaction, rather than an immediate wheal or reaginic response.

Correspondence with the National Drug Company revealed that rare reactions have occurred from intramuscular trypsin. These have occurred usually in patients who have developed localized erythema and induration at the site of administration, which on subsequent injections had grown larger. When therapy was continued beyond this, full-blown reactions have occurred. The reactions have been of the anaphylactoid type. The company also reports two cases with anaphylactoid reactions occurring when a second course of intramuscular trypsin was used three to six weeks after the patient had taken a course of injections without untoward effect.

Silbert[6] reported one case of an asthmatic woman who developed a diffuse rash about the pelvic girdle and an exacerbation of her asthma from repeated intramuscular trypsin.

In our patient it is quite possible that the one injection of intramuscular trypsin had already given her urticaria and the second buccal tablet was enough to throw her into severe asthma and shock. How much of her difficulty is due to the proteolytic action of trypsin and how much to antigen antibody reaction is impossible to state. Both may have been involved. Because of the violence of her reactions, we have been afraid to attempt to reproduce her symptoms by administration of another buccal tablet.

SUMMARY

An unusual case of urticaria, asthma, and vascular collapse which is felt to be due to therapeutic buccal trypsin is presented. There is an associated antibody to trypsin which is of the delayed type, and could be passively transferred. To our knowledge, this is the first such case reported, and the first time definite antibodies against trypsin have been demonstrated.

ACKNOWLEDGMENT

The authors wish to express their thanks to the National Drug Company for their cooperation in supplying the ingredients used for testing, as well as all information they had concerning reactions to therapeutic trypsin.

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Submitted May 25, 1959
Resubmitted June 11, 1959

ERRORS IN PSYCHOLOGY

The errors' size is lessened but not their number. Paradoxically, psychology—like other sciences, I imagine—makes a larger number of mistakes today than ever before. It asks more questions. For every question in psychology asked by the Greeks we ask a thousand. And the number grows. Every discovery breeds ten new problems. And every new answer is likely to be in some measure a mistake.

In general, then, more blunders of smaller size. And with them more truths and larger ones. The yearly balance-sheet shows a profit. But there is no greater error than that psychology now moves in clear truth, where earlier it moved in blind error. It always moved in both, and always will. But our opportunities of discovery are better than ever before. More psychologists, better trained, are at work. They use better technique. The experimental methods and the statistical methods greatly add to the power of the science. And each of these methods is daily refined and reshaped for the special problems of the field. New devices reduce the size of the errors that arise from personal prejudice and precipitance. And while there will perhaps always be a lunatic fringe to psychology, and a rebellious fringe and a reckless fringe, yet the central sane province is enlarged, extending our knowledge of the most important object open to science—the mind, and particularly the mind of man.—JOSEPH JASTROW, *The Story of Human Error.* New York, Appleton-Century Co., 1936.

POSSIBLE ALLERGIC CONDITIONS AFFECTING THE CENTRAL NERVOUS SYSTEM VIEWED FROM A NEUROLOGICAL STANDPOINT

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IN considering allergic conditions of the central nervous system, it is essential that the subject be examined critically in the light of modern neuro-immunological research evidence. Consideration will be limited to two subjects: (1) Migraine, and (2) Demyelinating Diseases of the Central Nervous System.

The problem of migraine headaches can best be approached from a neurological point of view. Certain basic neuroanatomical and neurophysiologic mechanisms, which are involved in the phenomenon of headaches, have been studied in recent years.

TABLE I. PAIN-SENSITIVE STRUCTURES AND PATHWAY OF REFERRED PAIN

Pain-sensitive Structures Head and Neck	*Final Common Pathway of Referred Pain*
Innervated by 5th cranial nerve	
Extracranial	
Eyes, sinuses, nose, mouth, middle ear, face, et cetera	Frontal scalp and face areas
Intracranial	
Large basal arteries, large veins of convexities, superior tentorium, dura about base of cerebral hemispheres	
Innervated by 9th and 10th cranial nerves	
Extracranial	
Throat and larynx	Occipital scalp and neck areas
Intracranial	
Dura of posterior fossa and inferior tentorium	
Innervated by the first three cervical nerves	

Studies by Wolff[1] and others have shown which structures of the head and neck, as well as intracranial structures, are pain-sensitive and also have shown the distribution of pain when these structures are stimulated. (Table I). In general, the pain-sensitive structures can be divided between the fifth cranial nerve with referral of pain to the frontal and facial regions, and the ninth and tenth cranial and the first three cervical nerves with referral of pain to the occiput and neck.

Mechanisms such as head injuries, tumors, aneurysms, lumbar puncture, and inflammatory processes in general, including allergy, may cause pain either directly or indirectly through stimulation of the pain-sensitive structures mentioned and along paths of referral, as outlined. Here the problem is a straightforward neurological one and, by means of careful history

Presented at the Fifteenth Annual Congress of The American College of Allergists, San Francisco, California, on March 16, 1959.

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taking, physical and neurological examinations, and special laboratory procedures, a correct diagnosis can usually be made. Depending upon the diagnosis, corrective measures may be instituted in a high percentage of cases. This is an extremely important class of headaches and patients with such headaches are frequently seen by the neurologist. Taken as a whole, however, such headaches constitute but a small percentage of all headaches.

A second group, which includes the patient with chronic and recurrent headaches that depend upon physiologic and psychic mechanisms, shows little in the way of abnormality on examination or when studied by special laboratory methods. The two main types of headaches in this group are migraine and tension headaches. Taken together, they account for a high percentage of all headaches. This, in addition to their chronic, recurring character, makes them of special interest and importance to all physicians who necessarily see many such cases, regardless of the exact nature of their practice. Because the general subject of headache is far too broad to cover here in any adequate fashion, I am limiting myself to a consideration of migraine.

MIGRAINE

In a study of 1,000 patients with migraine, Friedman[2] reported a familial incidence of 65 per cent with a 70 per cent incidence among women. Over 50 per cent of these patients suffered migraine before the age of twenty years, and its onset after age forty was exceptional. Headaches recurred less than once per week in 60 per cent of the patients, and prodromata occurred in 75 per cent.

No single factor would appear to be responsible for migraine, which of course greatly complicates the problem of management. Although it has a familial incidence in 65 per cent of cases, there is no evidence of the exact mode of inheritance, or as to what specific abnormality may be inherited.

The frequent association of migraine with puberty, menstruation, and menopause in women has suggested an endocrine factor, but here again, no definite evidence has been obtained to support this concept.

Water, sodium, potassium, and creatinine are known to be excreted in subnormal amounts prior to migraine attacks, while increased excretion develops as the headaches subside. This disturbance in water and electrolyte balance is not related to the onset, intensity, or duration of the headaches and is thought to be an adaptive reaction on the part of the body during stressful periods, rather than a causative mechanism.

Psychologic factors have been recognized and emphasized for many years. Initially, patients were considered to be stable between attacks, but subject to emotional reactions after certain vascular changes had developed. More recent studies, however, have indicated that the migraine

patient is apt to be a meticulous and overly-conscientious person, who is rigid and limited in his ability to adjust to the inevitable frustrations of life. However, not all patients are compulsive and inflexible perfectionists and also, such patterns are found in many who do not have migraine. Nevertheless, it would appear that psychological factors play an important role as conditioning and precipitating factors in migraine and, therefore, must be considered in the management of this condition.

Allergy has been advocated as an etiological mechanism for several generations, and there would appear to be no doubt that allergy can be a definite factor of primary importance. Many patients report that their attacks are related to known pollen and food allergens. Studies by Wolff with test doses of the known allergic factors in such patients have not given consistent results. Nevertheless, migraine secondary to food allergy —(for example, as a result of eating the Italian broad bean) has been well authenticated, and attacks related to other forms of allergy seem likely.[3]

It has been shown that migraine may be induced in patients prone to this type of headache by smaller doses of histamine than would be required in normal patients. Furthermore, the headache occurs on the side and in the area that is typical for the patient's clinical attacks. Since histamine has a vasodilatory effect and similar results have been obtained with other vasodilators,[4] it would appear that this is not a specific effect which can directly be related to an allergic mechanism. It has been shown that antihistaminic agents do not prevent or help clinical migraine headaches, although they block headaches experimentally induced by histamine.

As already implied, the underlying physiologic mechanism of headache is essentially nonspecific and will respond to many types of stimulation. It would seem likely, therefore, that in susceptible patients allergy might well serve as a conditioning mechanism or even precipitating mechanism. In the overall management of migraine, however, a complete study of all possible factors is essential, since mechanisms other than allergy can frequently be implicated. Only on such a basis may a rational therapy be established that will prove effective in at least the more severe and complex forms of migraine.

The pathologic physiology of migraine has been clearly linked with vascular mechanisms. A prodromal period characterized by such aurae as scotomata, photophobia, blurred vision, hemianopsia, paresthesia, and depression has been presumed to be related to focal cerebral ischemia and anoxia secondary to the constriction of various intracranial branches of the internal carotid arteries on one side or the other. A compensatory vasodilatation in other cranial arteries has been postulated either on the basis of a simple hydrostatic pressure effect caused by the initial constriction of certain cerebral arteries, or on the basis of a reflex mechanism concerned with the maintenance of cerebral homeostasis. Regardless of theory, the period of headache has been associated with vasodilatation

and an increased amplitude of pulsation of the extracranial arteries on the same side of the head. The arteries become sensitive and the pain is throbbing in character and accentuated by anything which raises the venous pressure, such as straining or stooping. Gastrointestinal symptoms, sweating, and other signs of autonomic instability characterize the second stage of migraine. In the third stage, the vessels and surrounding tissue become swollen and tender. The headache becomes steady, and during or following this stage, prolonged contraction of the neck muscles is apt to develop a tension headache, which thus complicates and prolongs the migraine attack.

The management of migraine can be discussed to best advantage under the headings of: (1) treatment of the attacks, and (2) prophylactic management.

TREATMENT OF ATTACKS

The principal agent used in the treatment of migraine attacks is ergotamine tartrate. This was first used by Eulenburg in 1873 and clinical experience has amply confirmed its efficacy and effectiveness in some 90 per cent of cases, providing it is used in adequate dosages in the early stages of attacks. Wolff and others have shown that ergotamine tartrate reduces the pulsation of the extracranial arteries approximately 50 per cent and this is presumed to be the basis of its therapeutic action.

The prophylactic management of migraine is of great importance and should be considered in every case. Allergic and endocrine factors should be considered and treated, if present. The clinical signs and symptoms of allergy and the methods of allergic therapy, however, are not within the province of the present subject.

If the headaches accompany menstruation, the use of progesterone or testosterone may be helpful. In some women, a low salt diet premenstrually along with a diuretic seems to be helpful. Diamox® or Diuril® in small doses each morning during the premenstrual period are of help in some women. The conditions of work and stress to which the patient is subjected must be considered. Adjustment of work conditions may be helpful and care must be taken to insure proper rest. It is particularly helpful if the tensions of the day are interrupted by a mid-day siesta. Along this same line psychotherapy may be indicated and in many cases this helps to reduce the frequency, duration and intensity of attacks. The tranquilizing agents have shown some promise in this group of headaches, but our experience so far permits no final evaluation. Sedatives are of limited help in this type of headache, and vasodilators have been of no value.

Another vascular type of headache, which is probably a variant of migraine, is histaminic cephalalgia. Several authors have felt that this form of headache is due to allergy. It has been shown to be associated

with the dilatation of the branches of the external carotid artery and to a lesser extent to portions of the intracranial circulation, which causes stimulation of pain-sensitive structures in the vessel walls or adjacent pain-sensitive structures.

Clinically, the pain occurs suddenly. It is severe and usually involves the orbital regions on one side, but may spread to become hemicranial in distribution. The pain is of short duration and sometimes less than 30 minutes. Lacrimation, injection of the conjunctiva, rhinorrhea, sweating, and facial erythema are apt to develop on the homolateral side. These intense headaches usually come at night or in the early morning and often follow a cyclic pattern, with daily or nightly attacks for several or many weeks, and then relief for months or even years before another cycle sets in. This type of headache occurs predominantly in white males and is commonly precipitated by alcohol.

One type which shows the cyclic incidence more clearly and which tends to develop under conditions of stress and strain when the patients are more susceptible has been singled out by Sir Charles Symonds under the designation of "cluster headache."[5] While the patient is susceptible, these headaches recur frequently and usually at night time, presumably when, with relaxation from the tensions of the day, the cerebral vessels pulsate over a wider oscillatory range and with dilatation sufficient to stimulate the pain-sensitive structures.

Three excellent reviews are now available[5,6,7] in the recent medical literature on these variant forms of migraine headaches and all agree that allergy probably is not the basic factor, as was previously thought. In many cases relief has not been obtained with histamine desensitization, antihistaminic therapy, or other allergic therapy.

In the "cluster headache" group improvement follows relief from conditions of stress and strain and, in the hands of some workers, with the use of ergotamine tartrate preparations taken in the evening or at bedtime. Sir Charles Symonds has advocated injections of ergotamine tartrate in this connection, but since rapidity of action is not a factor in this prophylactic form of therapy, adequate doses of ergotamine tablets by mouth or in combination with suppositories should be adequate. In my hands this has proved to be the case, although attention to other possible causative factors has also been given in the comprehensive management of this group of patients. The cyclic character of these headaches makes it difficult to evaluate the effectiveness of any single form of therapy, and it is on this basis that the earlier apparent success of histamine desensitization and other forms of allergic therapy has been questioned. Therapeutic evaluation is further complicated by the multiplicity of conditioning or precipitating factors to be found in most patients, and the difficulty of determining the relative benefit of any single therapeutic measure when more than one factor is influenced by

treatment or when comprehensive forms of management might benefit two or more causative mechanisms.

Regardless of this point, it is obvious that the possibility of allergy should be kept in mind in the overall study of patients with migraine headache. Tissue response to allergy is of a character which makes it an effective mechanism quite capable of triggering off the non-specific physiological mechanisms underlying the headache. This is true even of tension headache, where prolonged muscle contraction is presumably caused by emotional factors. That allergy may be a source of worry and tension is obvious, aside from any more specific physiologic effect it may have. The double role that allergy may thus play in headache problems must always be kept in mind. The possibility of allergic mechanisms should specifically be considered in all cases and if at all prominent as a factor in the overall study of each headache problem, should be ruled out by adequate follow-up allergy tests and desensitization therapy.

DEMYELINATING DISEASES OF THE CENTRAL NERVOUS SYSTEM

Ever since the neuroparalytic accidents of anti-rabic therapy, dating back over sixty years, the possibility of neurologic disease produced by parenteral injections of mammalian brain tissue has been accepted. The significance of this phenomenon, however, has only been more fully appreciated since it has become possible to develop such lesions quickly and regularly under controlled experimental conditions by means of the Freund adjuvant technique.[8] To begin with, therefore, it is important to review some of the essential features of experimental, allergic encephalomyelitis. The principal points to keep in mind in connection with experimental, allergic encephalomyelitis are as follows:

1. Central nervous system lesions can be produced regularly by a single, or by a few, parenteral injections of sterile homologous or heterologous brain tissue emulsified in paraffin oil and lanolin, fortified by heat-killed tubercle bacilli.

2. The emulsified base of paraffin and lanolin, which affords a mixture of several cholesterols, including oxycholesterol, is not an essential feature of this phenomenon, although their effect does enhance the reaction.

3. Experimentally, the heat-killed tubercle bacilli is the adjuvant of importance and it must be injected at the same site that the brain is injected. Other agents, such as BCG and certain other mycobacteria, also have been found to be fairly good adjuvants. A number of studies on biologically active fractions of various bacilli and on the essential biochemistry of the adjuvant have been made.[9,10] The main point is that the enhancing effect of the adjuvant constitutes the principal argument in favor of a sensitization mechanism being involved in the reaction. The use of adjuvants developed from their known enhancing effects on such simpler systems as sensitization to horse serum and egg white, and also in immu-

nization with diphtheria toxoid and bacterium typhosum. Adjuvants also have been found to raise the titres of complement-fixing antibodies tested *in vitro* with extracts of brain tissue on the sera of animals injected with brain.

It has been shown that experimental allergic encephalomyelitis may be produced in certain susceptible mammals without the benefit of an adjuvant.[10,11] In this case, however, it has been assumed that the equivalent of the adjuvant, possibly in the form of an old tuberculous infection, is already present in the animal. The old clinical observation of a predilection for Schilder's disease in patients with tuberculosis is of interest in this connection.

4. The active substance in the brain has been shown to be present in a wide variety of mammalian brains, including man, but not in those of fish or frogs.[12] The responsible factor has been studied at some length and has been found to be very stable. It is resistant to heat, drying, ultrasound, formalin fixation, and it may be stored for years. Biochemical studies suggest that it is either a protein or is protein bound.[13] Studies by Kabat[12] indicate that it appears in the newly born rabbit at the time of myelination of the cord and cerebrum and thus suggests that it is related to myelin.

5. Allergic encephalomyelitis may be produced experimentally in many mammals, including the monkey, but it is difficult to produce in the rat, which is notoriously difficult to sensitize.[13]

6. The lesion produced is peculiarly a neurologic one. Studies utilizing other tissues and organs have not been effective. Furthermore, when the brain is injected parenterally, only a brain lesion is produced.

Recent studies have shown that lesions of the peripheral nerves, nerve roots, and ganglia may be produced by injections of these same peripheral elements of the nervous system.[14] A different antigenic substance must be implicated in this case, since lesions of the central nervous system are not produced by peripheral nerve injections. If the active agent is related to myelin, the myelin of peripheral nerves is presumably different from that of the central nervous system. Other recent studies have suggested that this is true.

The lesions of the central nervous system produced in experimental, allergic encephalomyelitis are highly characteristic and consist of a cellular increase in the walls of the veins and venules in addition to varying degrees of microglial proliferation and demyelination in the perivenous tissue. The essential lesion would appear to consist of the cytological reaction in the wall of the veins. In all studies, the white matter has been chiefly affected. With severe involvement, confluent lesions of the whole white matter may occur with little or no involvement of the gray matter.

The same type of "perivenous" demyelination found in allergic enceph-

alomyelitis is very similar to the type found in man in the acute and disseminated forms of encephalomyelitis following such viral infections as measles, chickenpox, and smallpox, and also following vaccination against smallpox and rabies. Since neurotropic viruses do not cause demyelination, the presumption has been that this type of disease may be an allergic encephalomyelitis, as has been shown to be the case in the experimental animal. As recently pointed out by Lumsden,[15] however, the evidence for this thesis is by no means conclusive.

Nevertheless, the paralytic complications of the Pasteur treatment of anti-rabic vaccination using infected rabbit spinal cord provide a unique opportunity to study allergic disorders of the nervous system. Fourteen such patients were recently reported by Paul Levin[15] of Texas with an onset from nine to twenty days after the first inoculation. Diffuse meningoencephalomyelitis occurred in most instances. When mild, the picture was indistinguishable from "aseptic lymphocytic meningitis." Focal lesions were of myelitic, bulbar, pontocerebellar or cortical types. Peripheral involvement of the Guillain-Barré type occurred late in some cases. Corticosteroid therapy has been used with considerable success in this group.

Post-infectious encephalomyeloneuritis and "spontaneous" disseminated encephalomyelitis present the same picture and their probable basis as an allergic reaction is now fairly commonly accepted, even though the relationship has not been firmly established, as pointed out by Lumsden.[16]

The studies by Waksman and Adams[14] on rabbits are of particular interest, in that these workers have experimentally produced a condition which simulates in some respects the Guillain-Barré syndrome and Landry's ascending paralysis as found in man. Intradermal injections of rabbit sciatic nerve, or spinal ganglia, produced in the rabbit lesions in the peripheral nerves, spinal roots and spinal ganglia, associated with a marked increase of cerebrospinal fluid protein without an accompanying pleocytosis. Thus, both the pathology and the "dissociation albuminocytologique" of the human diseases mentioned have been mimicked by the experimental allergic condition produced by Waksman and Adams. Although not proof of an allergic basis for these conditions, the evidence at least is highly suggestive.

The evidence that other forms of demyelinating diseases may also be due to allergy is much less definite. The possible association of Schilder's disease and tuberculosis has already been mentioned with the implication that this might signify an allergic etiology of Schilder's disease. Since the pathology of this condition is a massive, confluent one involving large areas of the white matter, it is difficult to be sure what the early and primary nature of its neuropathology might be. Perivascular changes have been described, however, and it is possible that it has an allergic basis and is comparable to the massive and confluent type of demyelination that can be produced in experimental allergic encephalitis.

Neuromyelitis optica, or Devic's disease, is thought by most authors to be a fulminating form of demyelination related to multiple sclerosis and, therefore, may be considered in common with this disease.

Although allergy is often referred to as a possible cause of multiple sclerosis, the pathology of this condition is distinctly different from the perivenous demyelination obtained in experimental allergic encephalomeningitis. No allergen has been discovered in this condition and measures which are effective in allergic states, such as ACTH and antihistaminic agents, afford no protection in multiple sclerosis. Recognized forms of allergy are no more common among patients with multiple sclerosis than in the general population, and allergic desensitization in those patients who also have allergic diseases has not materially altered the course of the multiple sclerosis. Nevertheless, the possibility remains that multiple sclerosis may have an allergic basis and this theory forms the basis of several research efforts being made at present.

SUMMARY

Although the evidence is highly suggestive that the perivenous demyelination associated with acute encephalomyelitis following virus infections and vaccination may be the same as the allergic encephalomyelitis produced experimentally, final proof for this thesis is lacking.

There is evidence to suggest that the Guillain-Barré syndrome and Landry's paralysis may be a different type of allergic condition affecting the spinal roots and ganglia, but here again valid proof is lacking.

The evidence for an allergic basis in multiple sclerosis and the other forms of demyelinating diseases discussed is by no means definite.

The evidence that allergy is responsible for migraine is even less clear, since it would appear that the basic mechanism underlying this form of headache may be effectively stimulated by a number of nonspecific factors. Although allergy may well be one such factor, the successful treatment of this condition in the majority of patients, at least those showing more severe involvement, requires a comprehensive regimen established as a result of a careful study of all possible factors in each patient.

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Submitted May 4, 1959

ERROR IN PSYCHIATRY AND PHYSIOLOGY

The physiological conception admits that the phenomena of insanity are phenomena of consciousness, but it assumes that the mental processes are accompanied by corresponding changes in the brain, and to these brain changes it devotes all its attention. With the phenomena as facts of consciousness it has no immediate concern. The first aim of the physiological conception is to find the actual changes in the brain which occur in insanity and the brain changes correlated with each morbid mental process. Its ultimate aim is the discovery of convenient "laws" which will describe these brain processes in the shortest and most comprehensive manner. These laws will, of course, contain nothing but physiological terms—terms of consciousness will find no place therein.

The psychological conception, on the other hand, takes from the outset an altogether different route. It regards the conscious process occurring in insanity as the actual phenomena with which it is called upon to deal. Its ultimate aim is the discovery of convenient "laws" which will shortly and comprehensively describe these conscious processes. In this case the laws will contain nothing but psychological terms—terms of brain will find no place therein.

It is of the utmost importance that, in the final "laws" obtained by either the physiological or psychological conceptions, there should be no mixing of the terms. The physiological laws must contain no psychological terms, and the psychological laws must contain no physiological terms. Nothing but hopeless confusion can result from the mixture of "brain-cells" and "ideas." The reader must be asked to accept this statement as a dogma. And adequate demonstration of its truth would take us far beyond the limits of this book.—ABRAHAM MYERSON, (Editor), *The Story of Human Error.* New York, Appleton-Century Co., 1936.

EVALUATION OF EFFECTIVENESS, DOSAGE AND TOXICITY OF "PARA-BROMDYLAMINE MALEATE" IN ALLERGIC RHINITIS OF INFANTS AND CHILDREN

A Clinical Study in 200 Cases

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THE THERAPEUTIC value of antihistaminic agents for the symptomatic control of hayfever, urticaria, perennial allergic rhinitis, and several other of the allergic diatheses has been well documented, although the exact mechanism by which these agents "block" histamine in the allergic reaction is still unknown. There is some evidence[1] that these agents prevent access of histamine to receptor sites on cells thereby blocking normal cellular response to histamine. It has been theorized that antihistamine will occupy receptor sites without causing cellular response. No demonstrable chemical reaction or antagonism has been shown between histamine and antihistaminic agents nor do these agents prevent the release of histamine from cells in response to injury.

Although a number of good antihistaminic agents, at least by present standards, are known and utilized, research continues for effective histamine antagonists of low toxicity with effective and prolonged activity. In addition to the search for improved antihistamines, this effort seems justified due to marked individual variation among patients regarding action and undesirable side effects of these drugs; thus the need of having a number of preparations available with similar but not identical properties from which to choose. Also, reports[2,3,4,5,6] of serious reactions to certain of these drugs are increasing so that research to produce more effective yet less toxic compounds seems warranted.

The purpose of this study was to determine the effectiveness, minimal dose by body weight, tolerance and toxicity of an antihistamine from the monamine group for symptomatic relief of allergic nasal symptoms (stuffiness, itching, rubbing, watering, "snorting," "hawking," et cetera) in the pediatric age group. Little dosage and/or therapeutic data exist for any antihistamine specifically for this age group, especially for infants. Patients used in this study were those referred for treatment to the Allergy Section

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Presented at the Fifteenth Annual Congress of The American College of Allergists, San Francisco, California, on March 20, 1959.

of the Junior League Clinic, Texas Children's Hospital, and from our private practice. We elected to use a relatively new compound, Para-bromdylamine Maleate (Dimetane®*), which in several previous reports[7,8,9] apparently was highly effective and of relatively low toxicity. The structural formula of Para-bromdylamine Maleate is shown in Figure 1.

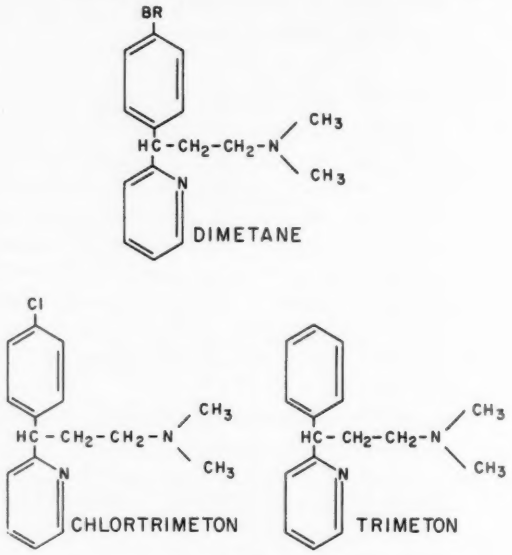

Fig. 1.

The molecular structure of Dimetane places it in group III classification of Syler and Marsh.[10] Included in this group are other commonly used antihistamines with a monamine structure such as Chlorprophenpyridamine (Chlor-Trimeton®), Prophenpyridamine (Trimeton®) and the dextro isomer of Chlorprophenpyridamine, Dextro-Chlorpheniramine (Polaramine®). It is to be noted in Figure 1, that Chlor-Trimeton has a chlorine molecule added to the basic Trimeton radical, and that in Dimetane a bromine molecule has been substituted in the same position. Studies[11] have shown that the bromine molecule in this compound does not lead to an elevation of blood bromide levels and, to our knowledge, no cases of bromism have been reported with its use.

Extensive studies in laboratory animals have shown Dimetane to be a highly potent histamine antagonist of low toxicity.[12] Results of clinicial trials with this antihistamine have been reported by ninety-four investigators in 1959 patients for the most part adults.[7,8,9] Findings were reported as good in 80 per cent of cases, fair in 8.5 per cent, and lacking

*Dimetane® used in this study was supplied through the courtesy of Dr. James O. Burke, Medical Department, A. H. Robins Co., Inc., Richmond, Virginia.

in benefit in 8.3 per cent. Of the patients studied, 6.6 per cent showed undesirable side effects, especially drowsiness. Conclusions based on grouping of data of this sort, of course, may be most unreliable.

During the past eighteen months, we have given Dimetane as an elixir

TABLE I. RESPONSE OF PERENNIAL ALLERGIC RHINITIS (PAR) TO PARABROMDYLAMINE MALEATE

Age—Two Months to Two Years

Disease	No.	Male	Female	Good	Fair	Poor
PAR	23	8	15	22	1	1
PAR and Asthma	23	16	7	20	2	1
PAR and Eczema	12	5	7	7	4	1
PAR, Asthma, and Eczema	15	8	7	6	6	2
TOTAL	73	37	36	55	13	5

(2 mgm/5cc) to 485 infants and children with various allergic manifestations, proved by history, physical findings, laboratory tests (nasal and/or peripheral blood eosinophilia), and specific skin tests with controls. Each of these patients had received environmental control instructions and many were receiving hyposensitization injection therapy against specific airborne allergens according to a tsandardized regimen. Over three-fourths of these patients previously had been treated with various other antihistaminic agents with slight or no relief of symptoms. Two hundred patients with perennial allergic rhinitis were selected by alternate allocation at the start of Dimetane therapy for careful follow-up studies. Many of these patients had some predictable seasonal exacerbation of their symptoms and thus perhaps could have had the term "hay fever" applied to them also. No child in this series had isolated, repetitive seasonal rhinitis alone, *i.e.*, classical fall hay fever. Each patient and/or parent was questioned repeatedly for any changes in allergic symptoms throughout the period of this study and patients were observed at one- to two-week intervals. These observations were made and graded independently by two observers. Results with respect to nasal symptoms were grouped as follows:

Good.—If virtually complete or highly significant relief of symptoms occurred and lasted several or more hours with no signs of toxicity or idiosyncracy to the drug.

Fair.—If there was some significant but less than highly significant subjective and/or objective improvement, with no signs of toxicity or idiosyncracy to the drug.

Poor.—If there was minimal or no subjective and/or objective improvement, or if undesirable side effects were present.

For purposes of noting age differences and determining dosage schedules, our patients were divided by age into three groups: Infancy—two months

TABLE II. RESPONSE OF PERENNIAL ALLERGIC RHINITIS (PAR) TO PARABROMDYLAMINE MALEATE

Age—Two Years to Six Years

Disease	No.	Male	Female	Good	Fair	Poor
PAR	28	13	15	18	7	3
PAR and Asthma	25	14	11	17	6	2
PAR and Eczema	9	8	1	8	1	
PAR, Asthma, and Eczema	8	5	3	8		
TOTAL	70	40	30	51	14	5

to two years; pre-school age—two years to six years; and the school age—six years through fourteen years. Results are shown in Tables I, II, and III.

As may be seen in Table I, the largest number of treated patients in the infancy group had perennial allergic rhinitis with or without associated asthma. The increased ratio of male to female infants with asthma in our series corresponds to a previously noted higher incidence of asthma in males in the young age group.[13]

The minimal and usually effective dose of Dimetane in infancy was found to be 0.2 mgm/lb./24 hrs. given in three divided doses. With many infants, however, it was necessary to increase the dose to 0.5 mgm/lb./24 hrs. before beneficial effects were noted.

By our classification, good responses for nasal symptoms were obtained in fifty-five of the seventy-three infants, fair responses in thirteen, and poor to no benefit in five. No undesirable side effects were noted in any patient from this age group, including those who received the much higher doses.

The minimal and usually effective dose for nasal symptoms in the pre-school age group was 0.2 mgm/lb./24 hrs. Fewer of these patients required larger amounts of the drug. As may be seen in Table II, good response was obtained in fifty-one pre-school children, fair response in fourteen, and poor or no response in five. Three patients were noted to have mild drowsiness although not severe enough to require diminution or discon-

tinuance of the drug. One six-year-old boy with perennial allergic rhinitis apparently received no benefit from one teaspoonful of the drug three times per day. His mother, without instruction from us, then increased the dosage to one *tablespoonful* four times a day (0.8 mgm/lb./24 hrs.) He

TABLE III. RESPONSE OF PERENNIAL ALLERGIC RHINITIS (PAR) TO PARABROMDYLAMINE MALEATE

Age—Six Years to Fourteen Years

Disease	No.	Male	Female	Good	Fair	Poor
PAR	16	9	7	12	4	
PAR and Asthma	21	13	8	16	5	
PAR and Eczema	13	7	6	11	2	
PAR, Asthma, and Eczema	7	2	5	4	2	1
TOTAL	57	31	26	43	13	1

immediately obtained good symptomatic relief of nasal stuffiness at this dosage, which was maintained for four months with continued relief and no apparent signs of toxicity.

The minimal and usually effective dose required for beneficial results of perennial allergic rhinitis in the school-age group was 0.15/mgm/lb./24 hrs. It is noted in Table III that a good response was achieved in forty-three patients, fair response in thirteen, and a poor response in one patient. The one poor result was due, in part at least, to excessive drowsiness, because of which the drug was discontinued.

All patients had initial blood studies and repeated blood studies were done on the majority of patients who had taken Dimetane for longer than three months. In no instance was there a significant change in hemoglobin, white blood cell count, or in differential white cell counts. No symptoms were noted to suggest clinical bromism; this included patients who had taken the compound daily for as long as fourteen months.

Since young children are peculiarly susceptible to the convulsive properties of certain antihistaminic compounds,[1] two cases are of particular interest. One two-year-old boy accidentally drank five ounces of Dimetane elixir (60 mgm or 2.0 mgm/lb.) yet suffered no apparent side effects. Another four-year-old boy drank eight ounces of the drug (96 mgm or 2.5 mgm/lb.) and the only noted side effect was mild, transient drowsiness. A recent report by Thomas[14] evaluating the injectable form of Dimetane in the treatment of acutely ill patients, refers to one adult patient, who

after receiving intramuscularly by error 100 mgm of the drug, showed no signs of toxicity. One should consider, however, that just as individuals show marked variance for therapeutic response to antihistaminic agents or other drugs, they may also show variation in their susceptibility to poisoning by these drugs. Although intoxication usually results from a large single dose, deaths have been reported from as little as 100 mg. of Diphenhydramine hydrochloride (Benadryl®[15]),

DISCUSSION

As stated, the primary purpose of this study was to determine the minimal effective dose of, and the presence or absence of untoward reactions in infants and children to Dimetane, a relatively new and representative antihistaminic agent of the monamine type. We realize that data from a clinical study of this kind is most difficult to obtain with accuracy for many reasons, such as physician and/or patient bias. Also, efforts by physicians to accurately evaluate subjective and objective data elicited from patients are never completely satisfactory. In spite of these inherent difficulties, and taking them into consideration, we believe that certain conclusions seem justified from this study. They are that Parabromdylamine Maleate is for the most part a safe, well-tolerated, and effective antihistaminic agent for the treatment of nasal allergies in infants and children when dosage is adjusted to weight or body-surface area.

In infants, a more physiologic measure of drug dosage than on the basis of body-weight is by the use of total body-surface area. Since infants have *more total body-surface area as compared to body-weight* than do adults or older children, the resulting dosage per pound is correspondingly increased for many drugs. For Parabromdylamine Maleate, approximately 10 mgm per square meter body-surface area represents our observed minimal and usually effective daily dose requirement for all ages. The use of total body-surface area illustrates what was observed in this study; namely, that relatively larger mgm per-pound doses were necessary in infants as compared to older children.

In previous studies with Dimetane, predominantly in adults, drowsiness has been observed in approximately six per cent of cases. Lipman[16] states that Dimetane and Chlor-Trimeton are about equally effective in controlling allergic symptoms, but that the incidence of side-reactions to Dimetane was significantly lower than to Chlor-Trimeton. The striking lack of hypnotic reactions noted in our study, (seven patients out of 200, or 3.5 per cent), suggests that infants and children are even less susceptible than are older patients to the sedative properties of Dimetane.

No actual "tolerance" was observed in any of the patients studied, even in those who had received the drug for as long as fourteen months. There were several patients whose response to the drug seemed to vary from time to time; this most likely may be explained by spontaneous increase or decrease in activity of the disease process or, as suggested by Vaughn,[17] for

other drugs, by an atypical response on the part of patients partially or completely independent of the drug. Also, factors inherent in the age of young patients are known to modify reaction patterns.[18]

The low incidence of toxicity and absence of "tolerance" with the higher dosage schedules used in our study suggest that considerably larger amounts of Dimetane than those usually recommended should be tried in infants and children in whom only minimal benefit has been obtained with generally prescribed doses. From our results, this would appear to be especially likely in infants, for in this age group the dose on a per-pound basis often had to be maintained at twice that dose on a per-pound basis for older children before beneficial results were obtained.

Possible explanation is perhaps in order for the high incidence of perennial allergic rhinitis and very low incidence of seasonal rhinitis (hay fever) in our series of infants and children. In our Gulf Coast area, the pollenating seasons are of long duration and mold growth is abundant perennially. In a multiple correlation study of 401 children,[19] which included a large number of patients in this current study, mold spores were found to be a major allergen, and perennial allergic rhinitis by far the dominant nasal allergy.

SUMMARY AND CONCLUSIONS

1. Dimetane is a safe, effective antihistaminic agent with a very low incidence of undesirable side effects in infants and children. With its use for the treatment of 200 children with perennial allergic rhinitis, good results were obtained in 149; fair results in forty; and poor results in eleven. Only seven patients demonstrated side effects, and in all except one the manifestion was mild drowsiness. In that one child, the drowsiness was more marked and necessitated discontinuance of the drug.

2. Dimetane was as effective for infants and young children as for older children, provided the dose for infants was adjusted upward on a body-weight basis. The average minimal effective dose for all ages studied was 0.2 mgm/lb./24 hrs. In infants, however, larger doses, even up to 0.5 mgm/lb./24 hrs., often were required before maximum benefit was obtained.

3. In three cases of marked over-ingestion, no symptoms suggesting central nervous system stimulation or other toxic symptoms were noted, such as those which have been described with other antihistaminic agents.

4. No symptoms suggesting clinical bromism were noted in three cases of over-ingestion or in those patients who had been receiving the drug daily for as long as fourteen months. Also, there was no alteration in their hemoglobin, total leukocyte, or differential white cell counts.

ACKNOWLEDGMENT

The authors are greatly indebted to Mrs. Martha Wilcox, Mrs. Jessie Busy and Mrs. Katherine Smith for their assistance in this study.

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Submitted June 24, 1959

HONESTY IN SCIENCE

"The success of the scientific method . . . is based entirely upon an absolute honesty of mind and love of truth . . .

"Dogmatic prejudice, lying falsification of facts, and data, and willful fallacious reasoning are all out of harmony with the spirit of the sciences. It is writ large in the history of science that the most heinous offense a man can commit is to falsify his data and let his prejudice and his desires color his reasoning. It has never been given to such a type of mind to discover any of the important truths of nature. If a student leaves his course in physical science with the typical scientific point of view, he has obtained a moral value which will be a distinct asset and which will help to lead him to a happy and successful life."—L. L. HENDREN, *Survey of Elementary Physics*, Athens, Georgia, The University of Georgia Press.

THE CENTENNIAL OF POLLEN AEROBIOLOGY

An Evalaution of Apparatus and Techniques

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A SCIENTIST found himself sneezing violently a few moments after examining a bouquet of bluegrass blossoms that had been placed in a closed room the day before by one of his children. Because he was a sufferer with "summer catarrh" and because he had seen the cloud of pollen rise into his face from the disturbed flowers, his mind began grinding out questions about the possible relation of air-borne pollen to his paroxysm. Although he did not then believe in the pollen theory, he considered it his duty to investigate the idea thoroughly. Thus, one hundred years ago, in May, Dr. Charles Blackley, pioneer aerobiologist, was led to address himself to problems that were to occupy his mind and hands all the rest of his life, "as occasion afforded." The investigations started by Doctor Blackley are still going on, otherwise this presentation would not have been planned by your program committee. Now it is my duty to report briefly on the snail-pace progress that pollen aerobiology has made in a century noted for amazing speeds in the development of many other sciences.

Blackley sensed the need of a method for rapid determination of a hay fever patient's approximate intake of pollen in a single breath or in the course of a few hours or during a whole day—in short, a volumetric sampler for determining the approximate number of grains of pollen in a known volume of contaminated air. He built spot samplers and air filters, but after eight years of experimenting he could say only that he had found the grass pollen content of the air of his home locality to be greater in the morning hours than at any other time of day, and the incidence in the country to be greater than in the city. He had found no satisfactory solution to his volumetric problem, so he turned to a simpler method of air sampling. In the spring of 1867, he began a series of daily exposures of glycerin-coated slides, in the center of a ten-acre meadow. The slide shelter was set at "nose level." In counting, he scanned a 1 sq. cm. area on each of four simultaneously exposed slides and used the average of the four counts as a unit of record.[1]

One approach that the ingenious doctor seems never to have tried was that of computing volumetric equivalents for his 1 sq. cm. counts. This was the contribution of that most enthusiastic botanist-physician, William Scheppegrell of New Orleans, who had started atmospheric pollen sampling with "gravity" slides in 1916. With the help of a teacher of mathe-

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Chairman of the Pollen and Mold Committee, Research Council, American Academy of Allergy.

matics, he attempted to apply Stokes' Law on the rate of fall of microscopic particles and came up with a table of factors for calculating cubic-yard equivalents from the 1 sq. cm. area counts on his slides. A single factor was needed for ragweed pollen, but because other kinds of pollen differ in size and rate of fall, separate factors were necessary for each kind. Doctor Scheppegrell sincerely believed that by using his factor of 1.8 one could quickly change a square centimeter ragweed pollen reading on a twenty-four-hour gravity slide into the correct average number of ragweed pollen grains per cubic yard of air.[2] So for pollen counting involving only ragweed pollen, it was sufficient to simply count an area of 1.8 sq. cm. and record the count as the "number per cubic yard of air." No one questioned the accuracy of the figures, at least openly, for twenty years after they were released, but some workers must have had their serious doubts.

As long as nationwide pollen studies were chiefly concerned with ragweed pollen, the 1.8 sq. cm. unit of counting and statement was not particularly objectionable. But as soon as counting in any locality was extended to species other than ragweed, it became necessary to apply the different factors to the slide counts for each of the other kinds of pollen that were found, regardless of what unit of counting area was used. To save the extra labor this would have involved, it soon became the common practice to dispense with the "per cubic yard" designation, even for ragweed pollen, and to report counts for all species of pollen as the number "per 1.8 sq. cm. unit area." One reason for this was that a change to any other unit for statement would necessitate working over a large accumulation of ragweed data over a period of years.

During this era, a newcomer in the field of pollen investigation was likely to adopt any unit that seemed reasonable or convenient to him. So it came about that different workers were using units ranging from 1 sq. cm. to 1 sq. ft. Of course, no one ever dreamed of scanning a square foot of slide area to obtain a twenty-four-hour count, but there was no law against calculating the amount of fallout on a square foot by multiplying the square centimeter figure by a thousand!

Into this confusion, a university professor, Dr. Elton C. Cocke, quietly dropped a bombshell (1937).[3] He had gone over Doctor Scheppegrell's calculations and found that because of one serious mathematical error and an unwarranted assumption, all of the published factors were grossly in error. When he had corrected these errors to his own satisfaction, he promptly set up a complete new set of factors. Soon afterward, he offered a small amount of experimental data to prove that his factors were reliable. In conclusion, he said, "The gravity method for determining pollen concentration of the atmosphere gives a true picture of the actual pollen concentration as shown by actual experiment."[4] Strange to say, there were those who thought his conclusion was mostly wishful thinking.

A few years later, Dr. A. O. Dahl, of the University of Minnesota, found and corrected some small errors in the Cocke factors but concluded that after all it would be better not to use any figures arrived at by dependence on Stokes' Law formulae.[5] As his reason for this decision he noted the lack of any basic experimental data on the density (specific gravity) of pollen grains. These should have entered into the Scheppegrell-Cocke calculations. He also pointed out the more serious lack of experimental data on the behavior of pollen grains suspended in turbulent, rather than still, air. He suggested that all aerobiologists would do well to state their findings on the basis of some acceptable unit slide area, regardless of any accompanying volumetric calculations that they might wish to present.

Meanwhile, another effort was made to defend the case for the much-abused conversion factors. Dr. R. C. Hawes[6] and two associates built a slit impinger volumetric pollen sampler (capacity 5 cu. ft. per hour) that promised to solve all problems of standardizing gravimetric counts. It was operated for 1820 hours during one long summer season in southern California simultaneously with the exposure of gravity slides, but unfortunately southern California did not afford airborne pollens of any kind in sufficient quantity for a statistical verification of the accuracy of the Scheppegrell-Cocke-Dahl factors. In a continuous twenty-six-day study, Hawes' average daily pollen catch (with the exception of one species of pollen on one windy day) was less than two pollen grains per species per cubic yard of air, and for any given species on the gravity slides about one-third of a pollen grain per square centimeter per day. Under such circumstances, Doctor Hawes was hardly justified in concluding that "It is confirmed that the Scheppegrell-Cocke formula for calculating pollen concentration from the results of gravity slide experiments is approximately correct."

For the next several seasons, the Hawes slit impinger was turned over to the author of this paper.[7] It was used during each ragweed season in runs averaging eight hours per day with a gravity slide exposed beside it. During the second season, a totally different type of volumetric sampler, the Keitt filter, was also operated in parallel with the impinger and the slide. This filter processed twelve times the quantity of air that passed through the Hawes impinger and gave remarkably similar readings for ragweed pollen contamination per cubic yard of air. Because of this most satisfactory agreement I accepted the volumetric day-by-day readings of the Hawes machine as accurate for all practical purposes. While it is still difficult to believe otherwise, there are experimental and theoretical reasons for caution. In these runs there was no attention paid to two factors which are now regarded as very significant—variations in wind velocity and the orientation of the intake orifice with relation to wind direction.

However, since the whole purpose of the studies was to determine ex-

perimental conversion factors, their success hinged on the correlation of volumetric counts with gravity slide counts. To our dismay, the day-by-day figures were most disappointing. For example, on August 25, 1942, the volumetric reading for ragweed pollen per cubic yard of air was 346, while the gravity slide caught 140 grains on a square centimeter. Thus the ratio—or factor—*for that day* was roughly 2.5. For the next day, the volumetric reading was 532 and the slide count only 29, which gave a ratio of 18.3 instead of 2.5. Which reading was in error and what could have caused the discrepancy, no one could possibly guess. On the second day, the wind velocity was only half that for the previous day and the wind had changed direction, but apparently these were not the only factors involved in the discrepancy which was evidently chargeable to the gravity slide. And this was not the maximum spread of the wild daily ratios. We did not expect perfection, but this seemed to be chaos. At least we now knew the worst, we thought, about the old standby gravimetric technique, and I was happy to be first to announce the bad news. Nevertheless, I found that at the end of the first season the *total* recovery by the two parallel runs yielded an *average* factor of 5.39 for 1942. In 1943, the ratio of totals was somewhat higher, 6.39 for the impinger and 6.71 for the filter device. The average for the impinger for three years was 4.9.

For the 1945 season,[8] instead of exposing the gravity slides on top of a thirty-inch steel rod as before, I used a newly devised covered shelter. During this season, the totals from the parallel tests gave a ratio of 3.6. This lower figure than that of previous years seemed to have been caused by the air turbulence induced by the "roof" over the slide.

While the earlier parellel tests were being run, I had busied myself with extensive experiments on the specific gravity[9] and rate of fall in still air of pollen grains of some forty species[10] of common hay fever pollens. Knowing that it would be impossible to do parallel volumetric-gravimetric tests over several seasons with forty other kinds of pollens in any quantity approaching that of ragweed, I decided to base the probable performance of other pollens falling on the gravity slides on my experience with ragweed, giving heed to their different densities and different rates of fall in still air. This, of course, led to setting up my own table of tentative approximate conversion factors.

My fellow members of the Pollen Committee took kindly to the idea of a standard exposure device for nationwide gravimetric sampling, but most of them shied away from another table of factors, except perhaps the ragweed factor of 3.6 for which there seemed to be reasonably good support. At least this scheme would keep newspaper figures somewhat uniform in meaning when published in the various larger cities where the public derives so much satisfaction from them. Even for the conversion of local ragweed figures, I recommended that each researcher should, if possible, run a series of parallel volumetric-gravimetric tests in his

own locality and thus determine his own local conversion factors. Thirteen years later come now Doctors Blumstein and Spiegelman,[11] who have the honor of being first to follow my recommendation. Their apparatus is the Marx impinger. In two seasons of volumetric-gravimetric parallel test in Philadelphia, even greater variance has been found in daily ratios than in my studies, and considerably higher seasonal average ratios. From a strict statistical standpoint, this would seem to be the *coup de grâce*—to all conversion factors, though not necessarily to the venerable glass slides. We know that gravity has little to do with the deposit of pollen on them, but we are a long way from understanding all the factors involved. Of course, Doctors Blumstein and Spiegelman do not hesitate to recommend that we abandon all thought of conversion factors. They agree, and so do I, with Doctor Vaughan, who long ago observed that to attempt to use converted, so-called cubic yard figures, gives the impression of a degree of accuracy which is far beyond the facts.

Meanwhile, other aerobiologists have been at work on the volumetric problem, both in America and in England. The Millipore filter method of recovery of pollen from the air, which has been tried out by several workers, offers considerable promise. It is inexpensive and simple to operate. But it has not been used in parallel runs with the Marx impinger or any similar instrument.

Dr. J. M. Hirst, of England, for a number of years has used an automatic spore trap[12] which seems to be equally useful for pollen grains and very small spores. This device is now being tried out in this country by Dr. Eugene Ogden and his associates at Brookhaven National Institute who are carrying on one of the most thorough investigations of pollen sampling methods and devices that has been attempted anywhere.

In the Marx impinger, we now seem to have a reliable sampler suitable for serious pollen research, but in the near future it should be subjected to critical testing for efficiency and accuracy. The ideal air sampler for routine daily air sampling has not been built—one that is inexpensive, simple to operate, and capable of delivering a twenty-four hour reading involving considerably less than an hour of tedious counting during times of heavy air pollution.

For the "gravity" or sedimentation method, it can still be said that although it does not yield accurate figures, it does indicate the time of onset, apex, and termination of seasonally abundant pollens. Seasonal totals have some comparative value. The slides reveal the presence of minor allergens in the air. Moreover, the increases or decreases in the daily fluctuation of pollen in the air as indicated by the volumetric devices are usually reflected in increases or decreases in the amount of pollen found on the gravity slide, even though the total volume of these fluctuations may differ greatly.

Two extensive and valuable state-wide pollen surveys have been made in recent years, one in Maine[13] and one in New York State.[14] In both

of these, the standard pollen shelter for gravity slides was used and the results were recorded on the 1 sq. cm. unit, with no attempt to use volumetric equivalents. The graphic presentation as used in both surveys is very effective.

In areas of strictly localized and meager pollen dispersal, such as southern Florida and most of California, spot testing of known wind-pollinated plants and suspected hay fever plant species to determine their individual maximum productive capacities will probably yield more useful information than the sketchy seasonal data obtainable with routine slide sampling. For this purpose, the Rotorod Sampler[15] developed at Stanford University seems to be ideal for short-period sampling up to one hour. This device is operated by a small 1½-volt D. C. motor, powered by dry batteries. It samples 120 liters (4.2 cu. ft.) of air per minute. Further research with modifications of the Rotorod Sampler is being carried on by Sheldon, Hewson, and Harrington[16] at the Engineering Research Institute at Ann Arbor, Michigan. These samplers are not yet available commercially. Meanwhile, my own hand-operated air whip,[17] or a modified form of it, may prove useful for spot sampling even though we do not now know what its samples mean in relation to the actual number of pollens per unit volume of air.

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Submitted June 16, 1959

TUBERCULOSIS AND RESPIRATORY DISEASES

Tuberculosis and other respiratory disorders are a leading cause of inactivity and absenteeism. These diseases are annually responsible for approximately one billion days of restricted activity; of 600,000,000 days of disability in bed; of 220,000,000 days lost from work; and of 196,000,000 days of absence from school.

The common cold, pneumonia, and influenza were responsible for more than half the acute respiratory diseases suffered during 1957, but tuberculosis alone is the most serious of the infectious diseases of the lung and respiratory system.

Today, approximately 250,000 Americans suffer from active tuberculosis. Another 1,750,000 are estimated to be inactively tuberculous. Forty million are carriers. Of the 40,000,000, the statistical odds are that 2,000,000 will, in time, suffer from active tuberculosis. These are some of the statistical numbers which were given study at the National Tuberculosis Association meeting in Chicago during May, 1959.

THEORY OF BODY PROPORTIONS

Yet the erect posture has brought not only advantages for man, but disadvantages as well. As a result of raising the head, the olfactory sense has become weaker, and the specifically human maladies (narrowing of the nasal chambers, deviations of the nasal septum, chronic catarrh) have appeared. In consequence of the erect posture, the internal dynamics of the body have been altered. Man has become a biped, but his body is built essentially like that of a quadruped, so that in relation to his internal organization his present posture is as unnatural as if an automobile should suddenly raise its front wheels in the air and begin to roll along on its back wheels. All the organs of the human body, the lungs, heart, blood-vessels, and digestive apparatus, were originally adjusted to a horizontal posture of the body and have suffered as a result of the transfer to an erect position. The aeration of the lungs has been impeded to some extent, and the apices of the lungs expand very little during normal respiration.—FRITZ KAHN, *Man in Structure and Function.* New York, Alfred A. Knopf, 1953.

ANAPHYLAXIS REACTIONS WITH PURIFIED PROTEINS FROM MILK

Historical Document

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In the course of a study of the proteins of cow's milk by one of us (Osborne, 1918), four proteins were isolated in a high degree of purity, and their individuality established by means of the anaphylactic reaction. Evidence of the essentially chemical basis of immunologic specificity, as emphasized in our previous communications on the immunologic reactions of the vegetable proteins (1913), thus received further support. Our experiments were performed chiefly to determine the chemical individuality of the various protein preparations under investigation, and the completeness of their separation from one another. However, since these results had an important bearing on problems of immunologic specificity, numerous additional experiments have been made from this standpoint with these carefully isolated proteins.

As one of the most readily available protein-containing solutions, milk, perhaps has been used in immunologic experiments with greater frequency than any other material except blood and egg white. The ease with which casein can be separated from milk in a relatively pure condition and its ready solubility in dilute alkali have made this protein particularly suitable for use when a pure isolated protein was desired. Hence many references are to be found in the literature dealing with the immunologic reactions of casein. It is evident, however, from the published accounts, that the casein used in much of this work was not so carefully purified as it should have been. Furthermore, in only a few instances in which the proteins of the whey* have been used, have these been separated from each other with the care necessary to secure sufficiently pure preparations. As we have found no complete review of the literature of the immunologic reactions of the several proteins of milk, we here present a brief synopsis in approximately chronologic order.

IMMUNOLOGIC EXPERIMENTS WITH MILK AND MILK PROTEINS

Although the earliest experimental work on immunologic reactions with protein solutions dates to 1897, apparently isolated casein was not used until 1901. Moro (1901), Hamburger (1901), and Levene (1901) independently, and almost simultaneously, published observations on the precipitin reactions with casein. Moro

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From the Pathological Laboratory, University of Chicago, and the Laboratory of the Connecticut Agricultural Experiment Station, New Haven, Connecticut.

*The term whey is here used to designate the solution of the milk solids from which casein has been removed by precipitation with acid.

reported that by immunizing with pure casein, from either human or cow's milk, he obtained a "specific lactoserum," but he did not describe its properties further. He also reported that precipitins for cow's milk gave reactions with goat's milk, but not with human milk, which was not in agreement with the earlier work on milk precipitins by Wassermann and Schutze (1901). The important observation was made that heating milk one-half hour at 100 degrees did not destroy its reactivity or its antigenic property.

Hamburger (1901) found that "lactalbumin" (which included all the proteins in solution after removing the casein) could be distinguished from casein by the precipitin reaction. Antilactalbumin serum (or, more properly, antiwhey serum) gave reactions with whole milk and with lactalbumin, but not with casein, and anticasein serum reacted with whole milk and casein, but not with whey. He prepared his casein by precipitating with acetic acid and then washing the precipitate free from "albumin." He also used Schlossmann's method of filtering off the casein through a "Thonzellenfilter," and stated that the "albumin" in the filtrate behaved somewhat differently from that obtained by precipitating out the casein.

In connection with other work, Levene (1901) merely reported that immune serum for milk gave precipitates with milk, casein, "milk albumin" and beef serum.

Fuld (1902) stated that whey obtained by filtering milk through porcelein filters did not react with antimilk serum. Since this is not in harmony with observations by others, it probably means that his immunization was sufficient to produce precipitins only for casein, and not for the other less abundant milk proteins. His statement that heated milk or casein solution did not produce precipitins has been shown to be incorrect. His antiserum for cow's milk did not react with goat's milk or with isolated casein from human milk.

Muller (1902), in a study of the relation of specific antiserum precipitins to rennin, observed that antimilk serum did not precipitate casein except in the presence of calcium salts, although it united with the casein in their absence. He found no evidence that the precipitation of casein by antiserum was accompanied by the splitting off of proteins similar to those of whey. In another article (1902) he stated that the products of digestion of casein with pepsin or trypsin did not produce precipitins either for themselves or for casein, although paracasein and iodocasein immunization gave precipitins that preciptiated casein. Lactoserum did not precipitate paracasein.

Gengou (1902) isolated casein, lactalbumin and lactoglobulin from cow's milk, finding that the casein and globulin gave complement fixation and precipitin reactions with antimilk serum, but the albumin did not react. The antiserum for cow's milk reacted with goat's and sheep's milk, and less strongly with human and horse's milk.

Schlossmann and Moro (1903), who discussed the methods used in the separation of milk proteins, recognized that the so-called milk "albumin" is a mixture of globulin and albumin, containing no phosphorus, which statement later studies have shown to be incorrect as far as globulin is concerned. They found also that the casein and albumin fractions each gave specific reactions for the species from which they were derived, and also that globulin from human serum reacted with anti-human-milk serum, but not with anticow's milk serum. Antiserum for human milk gave precipitates with human serum.

Amberg (1904), who reprecipitated his preparations, found that the precipitin reaction with milk or casein did not depend on the presence of either inorganic or casein salts of calcium, thus contradicting Müller. He observed no differences between the reaction with anticasein and antimilk serums when used against casein, milk, or lactalbumin.

Fleischer (1908) immunized animals with purified casein from animals of various

species (rabbit, cat, dog, horse, goat, cow and human), and found that the antiserums gave precipitin reactions with both the homologous and foreign caseins, although with quantitative differences in favor of the homologous caseins. Antiserum for cow's casein, gave about two-thirds as much precipitate with goat's casein as with cow's casein, and a good precipitate was obtained with horse's casein, but only a trace with dog's, cat's, and rabbit's casein, and none with human casein. Antiserum for human casein gave only relatively slight reactions with all the other caseins.

In their early studies of anaphylaxis, Rosenau and Anderson (1907) made some experiments with milk, obtaining no reactions when cow's milk was injected into guinea pigs that had been sensitized with either human or dog's milk, but positive results were given when the sensitization had been caused by sheep's milk. The first examination of isolated casein by means of the anaphylaxis reaction is reported by Besredka (1909), who stated that casein gave the same results as milk. The whey was found to sensitize to milk sometimes, but it did not always give reactions in animals sensitized to milk. Perhaps the difficulty here lies in the use of too small amounts of the whey (1/20 to 1/4 cc), which has a very small protein content.

Wells (1908) observed that purified casein was even more active in anaphylactic reactions than whole milk, for 0.1 to 0.125 gm of purified cow's casein usually produced fatal reactions when injected into the peritoneum of sensitized guinea pigs, while doses of 5 to 10 cc of whole milk containing 0.15 to 0.30 gm of casein were seldom followed by fatal reactions. The activity of casein solutions was not materially impaired by heating at 100 degrees for 25 minutes. Animals sensitized to goat's milk casein reacted severely when given cow's casein, or conversely, which agrees with Bordet's results with whole milk, and Fleischer's precipitin reactions with goat's and cow's casein.

A related observation on the lack of species specificity with casein is furnished by Michaelis and Rona (1909), who injected cow's casein subcutaneously into dogs and guinea pigs that had recently been actively secreting milk, and observed a notable swelling of the mammary glands, without marked constitutional symptoms. Some reaction was obtained in virgin animals. This they interpret as the production of a heightened secretory activity which induced the mammary glands to excrete the injected casein, although in none of the animals did actual secretion of milk follow the injection. On the other hand, Felländer (1912) was unable to sensitize guinea pigs to guinea pig's milk or to extracts of their mammary glands.

Bachrach (1910) failed to secure a good differentiation between casein, whey and beef serum by anaphylactic reactions. As he used the same sized doses for both sensitizing and intoxicating, his observations are not valuable.

The use of the complement fixation reaction with casein was introduced by Kollmeyer (1910), who obtained distinct differentiation of casein from whey by this method.

Graetz (1911) studied particularly the relation of milk to colostrum, and the only feature of his work of interest in this connection is the evidence obtained that colostrum whey contains proteins which seem to be identical with those of the serum. Other workers have obtained evidence of similar significance indicating the whey proteins to be closely related to the serum proteins. Thus, Bauer (1910) concluded that casein can be differentiated by complement fixation from the protein of the whey; that casein of different species of animals gives common group reactions, as also do the whey proteins, but that only the casein can be differentiated from the serum proteins of the same species. Bauereisen (1910) finds that the complement-fixation method like the precipitin reaction, does not permit an absolute differentiation of milk proteins from other proteins of the same individual, but that both methods show casein to be much less closely related to the serum proteins than

are serum proteins to whey proteins. He also recognized the probability that the failure to distinguish sharply between the isolated proteins depends on defects in the method of their preparation.

The quantitative differentiation of milk proteins demonstrable by complement fixation is great enough to be recognized by the less sensitive anaphylaxis reactions, as indicated by the results obtained by Kleinschmidt (1911). He separated casein, globulin and albumin from cow's milk, but in his description of the process used does not indicate that he reprecipitated his preparations. His "casein" was everything that came down with sufficient acetic acid; the "globulin" was the precipitate produced by saturating with magnesium sulfate after removing the casein with NaCl and the "albumin" was the precipitate obtained by adding acetic acid to the filtrate from the globulin. He found that anaphylaxis reactions (intracardiac) gave distinct differentiation between these three proteins. Casein sensitized to itself as well as whole milk, but did not sensitize to beef serum, lactalbumin or lactoglobulin. Experiments in the reverse order were almost equally specific. There were some slight crossed reactions, especially between globulin and casein, and a distinct protection (anti-anaphylaxis) reaction in all cases, probably due to incomplete separation of the proteins used. Guinea pigs sensitized with cow's casein did not react with human casein; no other foreign caseins were tried. Animals sensitized with either cow's lactalbumin or lactoglobulin with bovine serum, and conversely; those sensitized with lactalbumin reacted with lactoglobulin, and conversely. These last results do not warrant the statement made in the author's summary: "In anaphylaxis experiments the proteins of cow's milk, casein, albumin and globulin, can be differentiated from one another." There are quantitative differences in his reactions, to be sure, but those are not constant. It is quite evident that the author was working with imperfectly purified protein preparations. A similar difficulty is found in the work of Heuner (1911) who used commercial (Merck) cow's milk albumin and casein, as well as milk albumin and a globulin prepared by a chemist for him, the description not indicating that his preparations were thoroughly purified. Nevertheless, he also reached the conclusion that gobulin and albumin of milk are distinct from casein, and that colostrum and mastitis milk are more nearly related to the blood serum antigens than in normal milk. The differentiation was less marked in anaphylaxis experiments than with complement fixation.

Bauer and St. Engel (1911) separated casein, globulin and albumin in the same way as Kleinschmidt, but reprecipitated the globulin three times, although the albumin seems not to have been reprecipitated. Using the complement-fixation reaction, they found distinct quantitative differences between all three proteins. Thus, with an anticasein (bovine) serum, complement fixation was complete, or nearly so, in the following dilutions of 0.5 per cent solutions: casein, 1:256; globulin, 1:32; albumin, 1:16; milk, 1.64. With antiglobulin serum the figures were: casein, 1:8; albumin, 1:32; globulin, 1:16,384. With anti-albumin serum the figures were: casein, 1:1; globulin, 1:8; albumin, 1.64. Similar results were obtained with the globulin or casein of human milk. The proteins of one species were not tested against the antiserums for the other species. Cow's milk globulin could not be differentiated from beef serum globulin, hence these authors believed the globulin and albumin of milk or colostrum or serum to be identical.

Klein (1912) made a study of the nature of casein antiserum by the precipitin test, finding evidence that there are in such an antiserum two precipitins. One acts only in the presence of $CaCl_2$, while the other acts best in the absence of calcium. Hence the presence of two different antigen groups is postulated in the casein molecule. So far as we can learn, this important work has not been reinvestigated. The suggestion of the existence of two antigenic groups in a purified protein is, however, in harmony with the observations of Wells and Osborne (1913) with purified alcohol-soluble proteins from wheat, rye and barley.

In agreement with the results of Bauer and St. Engel, it was found by Kudicke and Sachs (1914) that under suitable conditions antimilk serum will, by virtue of the whey proteins, give complement-fixation reactions with blood serum of the same species, but if milk is boiled, the antiserum it engenders will react with milk but not with blood serum. (Evidently this depends on the coagulability of the whey and serum proteins and the incoagulability of casein.) Antiserum for bovine serum will give slight reactions with cow's milk boiled for not over ten minutes. Uhlenhuth and Haendel (1910) had previously found that boiled milk gave anaphylactic reactions only in animals sensitized with milk, whereas raw milk caused reactions in animals sensitized with either milk or serum of the same species.

Versell (1915) separated casein by adding acetic acid just short of precipitation, and then saturating the milk with CO_2; the precipitate was washed five times by centrifugation. The whey proteins were not separated from one another. Using the complement-fixation reaction, he found that antiserum for cow's milk reacted with goat's milk, but less strongly than with cow's milk, and more strongly than with human milk; the difference between the caseins of the three species was much less, and most between the wheys. Human milk antiserum gave reactions with human milk diluted to 1:31,250, with cow's milk at 1:1,250, with goat's milk at 1:50. Antiserums for milk or whey gave slight reactions with the serum of the same animal, but anticasein serum did not, as observed by Bauer and St. Engel, and Kudicke and Sachs; also heated casein was still antigenic but heated whey was not. Whey proteins showed the same degree of species specificity as blood serum, but casein showed much less species specificity, being rather in the class of the organ-specific proteins. He found the thermo-resistance of casein is only relative, for it is inactivated if heated sufficiently long or high.

Gay and Robertson (1912) found that isolated casein, as well as the "paranuclein" derived from it by peptic digestion, were both distinctly antigenic, one sensitizing against the other. Immunization with casein produced much more active precipitating and complement-fixing antiserums than did paranuclein, and these antiserums also reacted much more strongly with casein than with paranuclein. That is, partial peptic digestion reduced but did not destroy the antigenic power of casein. Completely digested casein was not antigenic. When united with protamine, it retained its antigenic power, the resulting antiserum reacting with either casein or protamine caseinate (1912). These authors believed that the paranuclein synthesized by the "reverse action" of pepsin on the products of peptic digestion of casein is an effective antigen, sensitizing and immunizing (complement fixation) both to itself and the paranuclein produced by partial peptic digestion, and thought that they had thus established the identity of the materials and also that synthesis of a true antigenic protein had been accomplished (1912).

The statement that casein is not an active antigen, made by Dale and Hartley (1916), is supported by the fact that injection of milk itself has been used extensively in nonspecific foreign protein therapy, ordinarily without harmful results, and Müller (1918) states that in an extensive experience he has never observed serious symptoms. However, the next article in the same journal, by Lubiner (1918) describes a nearly fatal reaction following intramuscular injection of 10 cc of milk into a girl, eight days after the last of three daily injections. Oppenheim (1917) also observed a similar case of severe reaction from milk. Of some interest may be the observation that the serum of parturient and lactating women produces a stronger positive Abderhalden reaction with casein than does the serum of men or normal or pregnant women (Kastan, 1914). Also we may mention that milk has hemolytic properties, as first shown by Bertarelli. Pfaundler and Moro found that it contains hemolytic complement. Bauer, Kopf and Sassenhagen observed that this is especially abundant in colostrum, which was corroborated by Schmidt (1911).

Taken all together, the results obtained by the several observers quoted seem to point definitely to the following conclusions:

1. Biologically, casein is quite as distinct from the whey proteins and the serum proteins as it is chemically.
2. The biologic reactions and chemical composition of caseins from different species of animals show close relationships.
3. The whey proteins as a whole are biologically similar to the soluble serum proteins of the animals from which they are derived. Colostrum contains a larger proportion of proteins of this type.
4. Casein from the milk of an animal of any given species shows a closer biologic relationship to the casein of another species than it does to either the whey proteins or to the serum proteins of its own species; the same is true of the chemical relations.

It is evident, however, that the amount of work done with proteins reasonably well isolated is as yet small, and in need of amplification and control.

THE CHEMISTRY OF MILK PROTEINS

In recent years the proteins of milk have received more careful study than previously, and several new facts must receive consideration in biologic work. Applying D. D. Van Slyk's amino nitrogen method, Crowther and Raistrick (1916) found that from the chemical standpoint casein, lactoglobulin and lactalbumin were sharply differentiated and distinct proteins, and that they have the same composition whether prepared from colostrum or from milk. Only 0.03 per cent of true globulin was found in milk; it was much more abundant in colostrum. As far as could be determined, the proteins designated as eulactoglobulin and pseudolactoglobulin are chemically identical. Lactoglobulin showed an amino-acid make-up similar to that of globulin from ox blood, but marked differences were found between lactalbumin and serum albumin. These observations correspond with the results of the immunologic demonstration that casein is distinct from the whey and that the latter possess features common to the serum proteins of the same species. A series of milkings made twice daily after calving were analyzed, the average composition of the milk from seven cows showing a steady drop in content of protein between the first and eighth milkings. [This] indicate(s) the relatively great abundance of globulin in colostrum, and its rapid reduction within the first 48 hours of lactation.

While caseins from different species do not show demonstrable quantitative or qualitative chemical differences by ordinary methods, a study of the products of racemization by Dakin's method yielded to Dudley and Woodman (1915) evidence of some structural differences. Caseins from sheep's and cow's milk consist of identical amino-acids, apparently in identical proportions, but when racemized the sheep's casein showed all the tyrosine and most of the lysine unracemized, while both were completely racemized in cow's casein.

Dale and Hartley (1916) state that caseins from different species show no clear disparity of antigenic properties, but it is possible that finer quantitative methods will disclose distinct discrepancies, as was found to be the case with the albumins from hen's eggs and duck's eggs. These same authors state that the antigenic properties of casein are relatively feeble.

Osborne and Wakeman (1918) found that the protein called lactoglobulin differed much in its solubilities from other globulins, and that it contained 0.24 per cent

of phosphorus, in which respect it resembled ovovitellin. In addition they obtained a small quantity of material that seemed to be a proteose, although not enough was obtained to permit positive identification. Of particular interest is the discovery that a protein is present in small amount in milk, which is readily soluble in 50-70 per cent alcohol. This alcohol-soluble milk protein in its content of amino-acids is distinctly different in composition from casein.

We, therefore, have chemical evidence that milk contains at least four chemically distinguishable proteins: (1) casein, characterized by a high content of phosphorus; (2) lactalbumin, a water-soluble protein which contains no phosphorus; (3) lactoglobulin, which contains 0.24 per cent of phosphorus; and (4) the alcohol soluble protein recently described by Osborne and Wakeman.

EXPERIMENTAL PART

Before describing our results we should first call attention to the fact that anaphylaxis experiments should be performed only with animals that have been raised on a known dietary which does not contain the proteins under investigation, and the same should be true of the mothers, since a certain amount of active immunization may result from the food proteins, which can be passively transferred to the fetus. It has been shown by one of us (Wells, 1911) that young guinea pigs fed on a given protein (egg white or milk) after a short time become sensitized to that protein so that they will give typical reactions when it is injected parenterally. If the feeding is long continued the animals become so immunized after a time that even a sensitizing injection of this protein will not render them hypersensitive, and a second injection has no effect. Guinea pigs raised largely on oats, therefore, do not give good reactions with oat proteins, although readily sensitized to other, unrelated vegetable proteins; and guinea pigs raised on corn were found not to serve for reactions with proteins from corn, although readily sensitized to oat proteins. Probably this fact accounts for numerous failures and irrational results obtained in anaphylaxis work, and must be taken into account, particularly in experiments with proteins such as those of milk, that might be present in the guinea pig dietary. In these experiments all our guinea pigs have been raised exclusively on a vegetable diet, as have their mothers.

In determining specificity it is also imperative that every precaution be taken to avoid contamination, especially of the sensitizing doses, with even the smallest possible quantity of the protein that is to be used for the intoxication dose. As numerous articles discussing anaphylactic specificity do not mention these precautions, leaving the reader uncertain as to the significance of the results described, we state explicitly that in this, as in all our work, such contaminations were rigidly excluded. All glassware, after thorough washing, is kept for at least 24 hours in concentrated sulphuric acid and potassium bichromate; the needles are most thoroughly cleaned and kept in absolute alcohol.

During the course of this work several preparations of various fractions, obtained in the isolation and purification of the milk proteins, were tested by means of the anaphylaxis reaction. The following tables give the results obtained with purified preparations of the four known proteins. The terms used are as defined in our previous work (1911). Unless otherwise specified the injections were made by the intraperitoneal route. The interval between sensitizing and intoxicating injections was usually about from 18 to 20 days. The references to protection indicate the protection of a sensitized animal against reinjection with the homologous antigen after previous injection of some heterologous antigen.

The first nineteen experiments recorded deal with the antigenic properties of casein. They show that, on the whole, casein is not so active as some other soluble proteins in producing anaphylactic sensitization and shock, but, on the other hand, its activity is by no means low. By intracardiac injection the minimum lethal dose is apparently between 0.000,02 and 0.00001 gram, but by intraperitoneal injection it requires nearer 0.010 gram to cause death, and 0.020 gram is not always fatal. Presumably this great difference in the efficiency of intracardiac and intraperitoneal injections of casein depends on the readiness with which casein is thrown out of solution, for with the vegetable proteins we have found that their intraperitoneal toxicity for sensitized animals seems to vary directly with their solubility in the body fluids (Wells and Osborne, 1914). As compared with its intoxicating power the sensitizing capacity seems to be very low.

Experiments 20 to 24 show how completely distinct these preparations of lactalbumin and casein are from one another. The same is shown for casein and lactoglobulin by experiments 25 to 28. Experiments 29 to 38 indicate that the alcohol soluble protein is quite distinct from casein, but that our alcohol soluble protein preparation probably contains a trace of casein, since with 5 mg sensitizing doses two of four animals gave severe reactions with casein. Since the alcohol soluble protein is obtained from casein by washing the precipitated casein with alcohol, this admixture is to be expected.

Experiments 39 to 42 indicate the absence in beef serum of appreciable amounts of any protein resembling casein. Elsewhere we have reported observations showing that casein will sensitize to milk, and conversely, as has been observed by others.

The first thirteen experiments . . . indicate that lactalbumin is an active anaphylactogenic substance, thus differing from the albumin fraction of horse serum, which according to numerous observers, is very defective in anaphylactogenic properties (Dale & Hartley, 1916). It is much less actively anaphylactogenic than egg albumin, but corresponds closely to casein.

Experiments 14 to 25 indicate that lactalbumin and lactoglobulin are

entirely distinct proteins, but that our preparations are not completely separated, for while 5 mg sensitizing doses give little or no crossed reactions, 50 mg sensitizing doses of either preparation will do so. As the globulin and albumin separations merely depend on the fact that the globulin comes down in a neutral saturated solution of magnesium sulphate, while the albumin is precipitated from the filtrate of this precipitation by acidification, it is remarkable to find that the separation can be made so nearly complete. The fact that we are here dealing with distinctly different proteins is certainly demonstrated. Experiments 26 to 30 show that lactalbumin is a distinct protein, and that it can be separated from casein almost perfectly.

The complete distinction of lactalbumin from the alcohol soluble protein is established by experiments 31 to 34, while the distinction from casein has already been commented on.

That the albumin fraction of cow's milk is distinct from the protein called albumin, or any other protein, of cow serum, is shown by experiments 35 to 38. This agrees with the demonstration by Crowther and Raistrick (1916) of the chemical distinction between bovine lactalbumin and bovine serum albumin.

Experiments 1 to 17 show that lactoglobulin is an active anaphylactogen. The experiments with casein and lactalbumin are the same as those in previous tables and have already been discussed. The individuality of lactoglobulin and the alcohol soluble protein of milk is established by experiments 34 to 37. Experiments 38 to 49 show that lactoglobulin differs from the other three protein fractions of milk, since even in 1 mg doses it sensitizes effectively to beef serum, and also intoxicates animals sensitized with small amounts of beef serum, corroborating the results obtained with the complement-fixation reaction by Bauer and St. Engel (1911). We thus find that the earlier observations on the capacity of beef serum and cow's milk to sensitize to each other is due solely to the globulin of the milk. This fact is in gratifying agreement with the chemical observation of Crowther and Raistrick since it indicates that bovine lactoglobulin is chemically identical with the globulin fraction of beef serum, although lactalbumin and serum albumin appear to be chemically different proteins.

The observation of Heuner that colostrum is biologically more closely related to serum than later milk, harmonizes with the high globulin figure obtained in colostrum by Crowther and Raistrick. The fact that colostrum contains large amounts of globulin, that this globulin seems to be identical with serum globulin, and that the serum globulin fraction carries the antibodies of the blood, is in interesting agreement with observations that have been made which indicate that the suckling animal secures important accessions to its antibody defense during the first days of life (Reymann, 1920).

The previously reported observations that cow's milk and bovine serum are uncertain in their capacity to sensitize to one another is explained by the presence of a very small amount of globulin in milk, corresponding immunologically to serum globulin, for it has been shown by Julian H. Lewis (1915) that a small amount of one antigen injected together with another antigen in excessive amounts, may be completely or partly prevented from manifesting its antigenic activity. This probably explains the fact that in our experiments, 0.1 cc of beef serum sensitized more effectively than 1 cc.

We have discussed . . . the complete differentiation of alcohol soluble protein of milk from the three other protein fractions. It is to be recalled that this protein has only recently been described by Osborne and Wakeman, and that the application of the anaphylaxis reaction played an important part in the differentiation from the other proteins of milk. When large quantities of freshly precipitated casein were extracted at room temperature with 50-70 per cent ethyl alcohol, it was found that the alcohol had dissolved out a considerable quantity of protein. As hitherto the only known alcohol-soluble proteins were of vegetable origin, it was suspected that this material might be either a cleavage product or a derivative of the casein. The anaphylaxis test demonstrated that it was not a proteose or similar cleavage product, since these do not exhibit active anaphylactogenic properties as does this alcohol-soluble protein (Exper. 1 to 15), while cross sensitization as well as chemical tests showed that it was not casein. Further chemical study showed that it yielded a different proportion of some of the amino-acids than did casein and was, therefore, a newly recognized constituent of milk. Although resembling gliadin in solubility, it is chemically distinct from this protein and in agreement therewith yields negative results with cross sensitization tests with gliadin (Exper. 50 to 53). The positive cross experiments with milk indicate that it is a constituent of milk, and not formed by manipulation during isolation (Exper. 28 to 41). With such a relative excessive proportion of other proteins present in the milk, it is not to be expected that effective sensitization with milk can be obtained. The amounts of the alcohol soluble protein which give strong sensitization to milk are so small (3 to 4 mg) that sensitization with admixed casein seems to be excluded, since less than 1 mg doses of casein sensitize but little.

Experiments 54 to 57 indicate that beef serum does not contain the alcohol-soluble protein of milk.

SUMMARY

Cow's milk contains four chemically distinct proteins or protein fractions, namely, casein, lactalbumin, lactoglobulin and an alcohol-soluble protein. By means of the anaphylaxis test it can be shown that these 4 proteins are immunologically distinct. This fact furnishes another striking illustration of the dependence of immunologic specificity on chemical composi-

tion rather than biologic origin. Of these four proteins only one, the globulin, sensitizes to beef serum or causes reactions in animals sensitized to beef serum. This corresponds to the observation of Crowther and Raistrick that lactoglobulin and serum globulin are chemically indistinguishable. That some positive cross sensitizations may be occasionally obtained between cow's milk and beef serum is explained by the fact that the globulin constitutes a very small part of the milk proteins. Several other protein fractions obtained in studying milk proteins were, according to anaphylaxis tests, not distinct from the four known proteins of milk. Our experience with milk proteins, as well as with proteins of other sources, has demonstrated that immunologic methods are a great aid and in many cases indispensable in preparing proteins in a state of purity, and may be used to furnish information concerning chemical relations of proteins from different sources.

APPLICATION OF AVERAGES

"There is, of course, the other application of averages that is equally important: ten authorities estimate the magnitude of some measurable matter, or one authority makes ten estimates, and many or all of the results differ slightly from each other; if we have no reason to attach greater weight to one result than to another, experience shows us that the average of all the estimates is more likely to be right than any other value. In this usage, the average of mensuration, the mean represents a thing actually existing, and the more carefully the mean is derived the closer our concept comes to the reality; whereas in the first usage, the average of biological variation, the mean represents something that is non-existent, a mere product of our imagination, and the more carefully it is derived the more removed it is from reality, in that there is less probability of its being identified with any one individual. And for us as Aristotelians it is the individual that counts."—Homer W. Smith, *Plato and Clementine,* Morris Herzstein Lecture (III) delivered at the University of California, December 6, 1946.

Papers of Interest

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Clinical description of the syndrome which includes "a feeling of deep pressure" as heaviness in the thorax, or the "aerophagia which is commonly associated may cause distress in the chest." The disorder is considered to be psychiatric in nature and should be more often recognized in asthmatic patients.

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On the ninth day of treatment, the patient responded with giant urticaria and intermittent hydroarthrosis, pyrexia, tachycardia, and increased erythrocyte sedimentation rate, all of which responded to nine days of corticosteroid therapy.

Bernton, H. S.: The incidence of allergic disease in a prison population. Med. Ann. District of Columbia, XXVII, 8 (Aug.) 1958.
Of 1500 prisoners interviewed, 328, or 21.8 per cent, were allergic, with dermatologic allergy representing a percentage of 7.3, and allergic coryza, 1.7 per cent.

Josse, J., and Zacks, S.: Thymoma and pancytopenia. New England J. Med., 259:3,113 (July 17) 1958.
Rare concurrence to be kept in mind in cases of pancytopenia.

McMaster, P. R. B.: Auto-antibodies and autosensitivity. New York J. Med., 58:2980 (Sept. 15) 1958.
Auto-immunity may be implicated in sterility. The possibility of auto-immunity may be a factor in unsuspected diseases.

News Items

THE AMERICAN COLLEGE OF ALLERGISTS

NOMINATING COMMITTEE

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William H. Browning

Submitted for publication on November 3, 1959

THE NEW YORK ALLERGY SOCIETY

At the annual business meeting of The New York Allergy Society, held November 18, 1959, at the Hotel Beekman Tower, the following officers for the year of 1959-1960 were elected:

President.....S. Senior Sack, M.D.
President-Elect.....Joseph H. Fries, M.D.
Vice President.....Sheppard Siegal, M.D.
Secretary.....Ely Perlman, M.D.
Treasurer.....Murray Dworetzky, M.D.
Assistant Secretary-Treasurer.....Walter Kessler, M.D.

PITTSBURGH ALLERGY SOCIETY

At a recent meeting of the Pittsburgh Allergy Society, the following officers were elected for 1959-1961:

President.....Macy I. Levine, M.D.
Secretary-Treasurer.....Irwin A. Solow, M.D.

OREGON SOCIETY OF ALLERGY

Officers of the Oregon Society of Allergy, elected during September, 1959, are:

President.....George M. Robins, M.D.
Vice President.....George J. Schunk, M.D.
Secretary-Treasurer.....Alvin D. Wert, M.D.

NEWS ITEMS

FIRST BAHAMAS ALLERGY CONFERENCE

The First Bahamas Allergy Conference will take place at the Nassau Beach Lodge, Nassau in the Bahamas, from March 5 through March 12, 1960. Approximately forty speakers will talk on various phases of allergy, and there will be ample time for discussion. The meeting will follow the Sixteenth Annual Congress of The American College of Allergists which will be held at the Americana Hotel, Bal Harbour, Miami Beach, Florida, from February 28 through March 4, 1960.

INTERNATIONAL SYMPOSIUM OF DERMATOLOGY

A symposium on "Professional Dermatoses" will take place in Prague, Czechoslovakia, on October 12-15, 1960. Participating in this International Symposium of Dermatology will be the Czechoslovakian Association of Dermatologists, the Association of Dermatologists of the Bulgarian Democratic Republic, and the Association of Dermatologists of the German Democratic Republic, all in co-operation with the Czechoslovakian Society of Occupational Medicine and Allergology.

Inquiries may be addressed to the General Secretary of the symposium, Dr. Quido Hornstein, Dermatological Clinic, Medical School of Hygiene, Prague 12, Srobarova 50, Czechoslovakia.

CHANGE IN FREQUENCY OF PUBLICATION

With the publication of the January, 1960 number, ANNALS OF ALLERGY will become a monthly publication issued twelve times a year instead of six times as formerly. These twelve numbers will be available at the yearly subscription rate of $10.50, plus $2.00 for foreign postage.

Orders for renewal and new subscriptions should be addressed to ANNALS OF ALLERGY, 2642 University Avenue, Saint Paul 14, Minnesota.

HAZARDS OF NEW DRUGS

Hazards of therapy have been present since the earliest days of medical practice and many have been due to ignorance, but in spite of the great advances of medical science each new procedure or new drug seems to carry with it potential dangers. It therefore behooves every medical practitioner constantly to be on the alert for unexpected mishaps. Some may be due to lack of skill, some to lack of knowledge, whilst others appear to be unavoidable. It is therefore important to be acquainted with the possible risks of each new or unfamiliar drug or procedure and to have at hand the means to counteract any emergencies which may arise. If risks can be anticipated, it may be wise, in view of possible medico-legal repercussions, to warn the patient in advance. On the other hand, it is equally unwise to strike terror into the heart of a patient when risks are minimal.—From "Iatrogenic Emergencies," W. G. Sears, Mile End Hospital, London, England, *The Practitioner*, 182:450-456 (April) 1959.

OF AVERAGES

"By destroying the biological character of phenomena, the use of *averages* in physiology and medicine usually gives only apparent accuracy to the results. From our point of view, we may distinguish between several kinds of averages: physical averages, chemical averages and physiological and pathological averages. If, for instance, we observe the number of pulsations and the degree of blood pressure by means of the oscillations of a manometer throughout one day, and if we take the average of all our figures to get the true or average blood pressure and to learn the true or average number of pulsations, we shall simply have wrong numbers. In fact, the pulse decreases in number and intensity when we are fasting and increases during digestion or under different influences of movement and rest; all the biological characteristics of the phenomena disappear in the average. Chemical averages are also often used. If we collect a man's urine to analyse the average, we get an analysis of a urine which simply does not exist; for urine, when fasting, is different from urine during digestion. A startling instance of this kind was invented by a physiologist who took urine from a railroad station urinal where people of all nations passed and who believed he could thus present an analysis of average European urine!

Aside from physical and chemical, there are physiological averages, or what we might call average descriptions of phenomena, which are even more false. Let me assume that a physician collects a great many individual observations of a disease and that he makes an average description of symptoms observed in the individual cases; he will thus have a description that will never be matched in nature. So in physiology, we must never make average descriptions of experiments, because the true relations of phenomena disappear in the average; when dealing with complex and variable experiments, we must study their various circumstances, and then present our most perfect experiment as a type, which, however, still stands for true facts. In the cases just considered, averages must therefore be rejected, because they confuse, while aiming to unify, and distort while aiming to simplify. Averages are applicable only to reducing very slightly varying numerical data about clearly defined and *obsolutely simple cases* . . . I acknowledge my inability to understand why results taken from statistics are called *laws:* for in my opinion scientific law can be based only on certainty, on absolute determinism, not on probability. . . . In every science, we must recognize two classes of phenomena, first, those whose cause is already defined; next, those whose cause is still undefined. With phenomena whose cause is defined, statistics have nothing to do; they would even be absurd. As soon as the circumstances of an experiment are well known, we stop gathering statistics: we should not gather cases to learn how often water is made of oxygen and hydrogen; or when cutting the sciatic nerve, to learn how often the muscles to which it leads will be paralysed. The effect will occur always without exception, because the cause of the phenomena is accurately defined." (Claude Bernard, *Introduction ot the Study of Experimental Medicine)*

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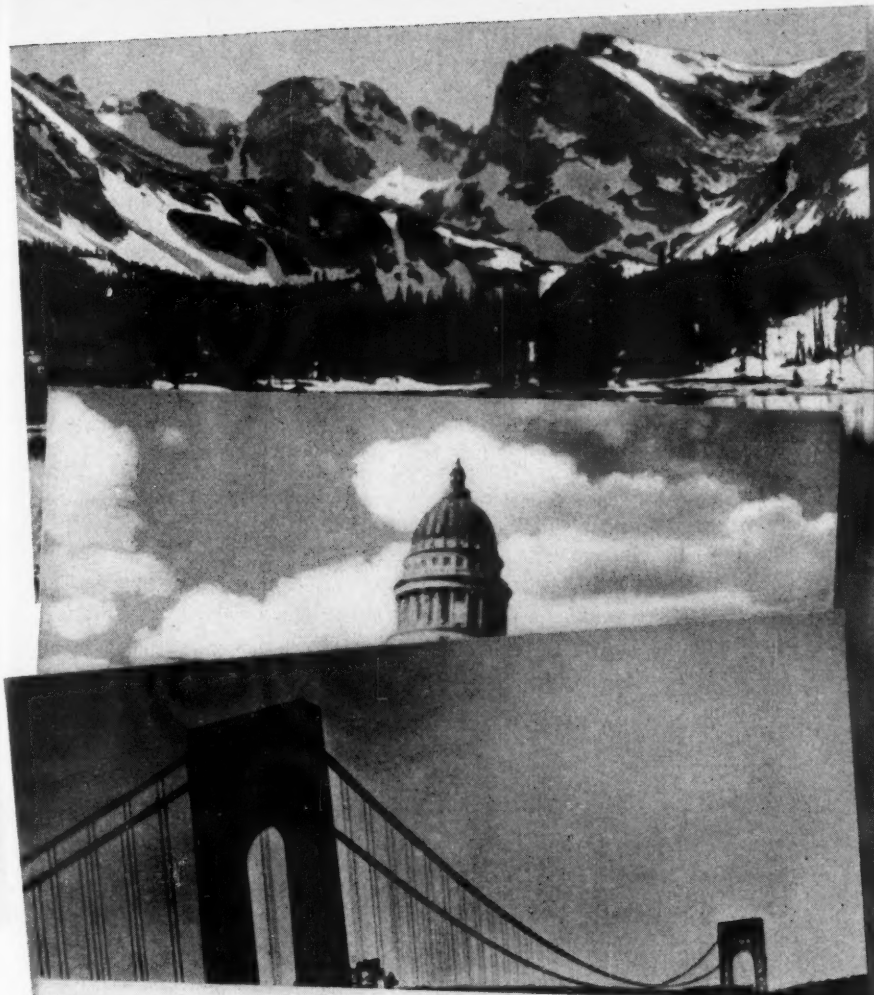

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ANNALS OF ALLERGY is published six times yearly by The American College of Allergists. Contributions which advance knowledge or understanding of the subject of allergy may be submitted for publication. Acceptable also are case reports, book reviews, editorials, news items, obituaries of Fellows, and historical documents.

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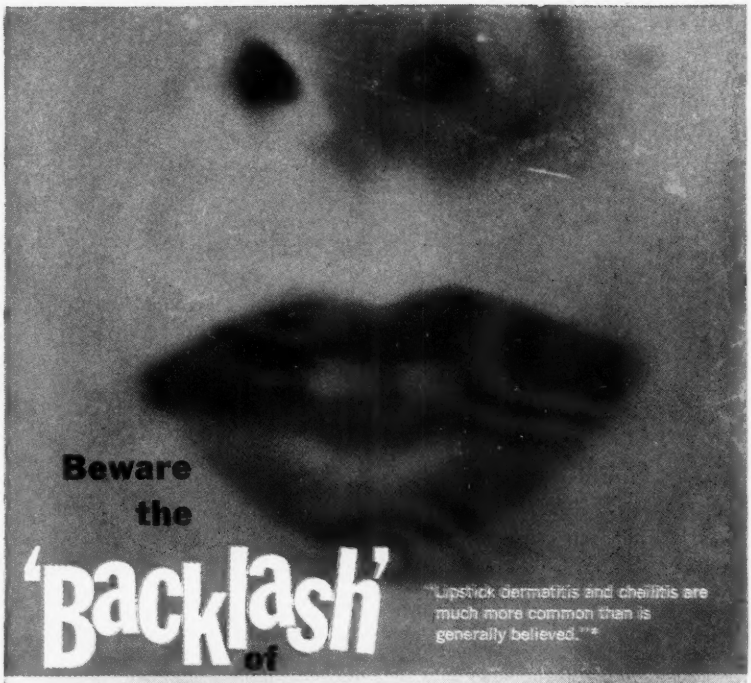

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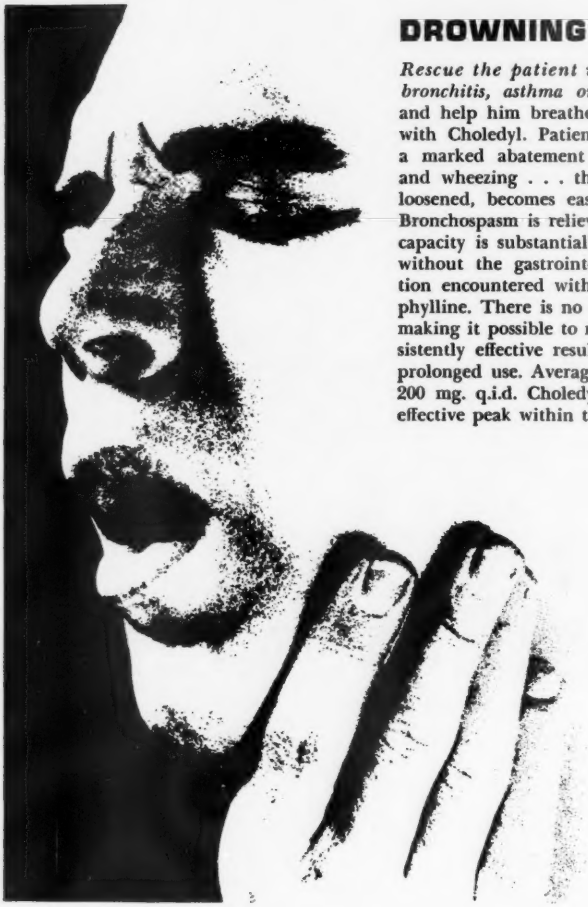

DROWNING IN AIR

Rescue the patient with chronic bronchitis, asthma or emphysema and help him breathe freely again with Choledyl. Patients experience a marked abatement in coughing and wheezing . . . thick mucus is loosened, becomes easier to expel. Bronchospasm is relieved, and vital capacity is substantially increased—without the gastrointestinal irritation encountered with oral aminophylline. There is no drug-fastness, making it possible to maintain consistently effective results even after prolonged use. Average adult dose: 200 mg. q.i.d. Choledyl reaches an effective peak within two weeks.

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MORRIS PLAINS, N.J.

betters breathing . . . forestalls the crisis

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brand of oxtriphylline

August isn't the only hay fever month* ... and there is no seasonal limit on the antiallergic action of Chlor-Trimeton® Repetabs® 8 or 12 mg.

safest, best tolerated, for both seasonal and nonseasonal allergies
the most prescribed antihistamine in the United States

Bottles of 100 and 1000.
SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

**in every month of the year there are allergenic pollens thriving in some part of the United States*

SYMBOL OF THE ONE-DOSE CONVENIENCE YOU WANT FOR YOUR PATIENT

PROMPT REPETAB RELIEF • LASTS ALL DAY OR NIGHT •

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CTM-J-125

In Canada—Omega Laboratories, Ltd., Montreal and Toronto
In Cuba—Laboratories Amedin, S.A., Habana
In Venezuela—Salus, C.A., Caracas

when holiday dinners include food allergens

BENADRYL®

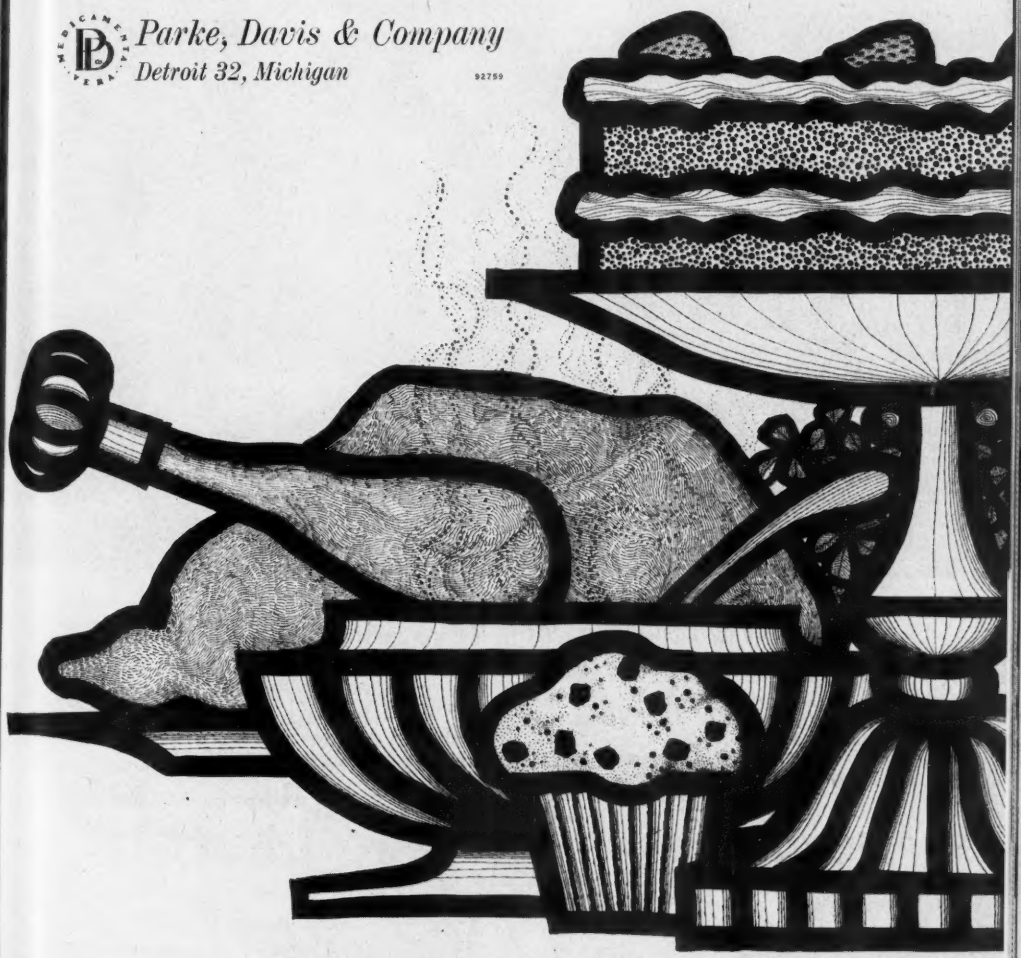
ANTIHISTAMINIC-ANTISPASMODIC

gives prompt, comprehensive relief

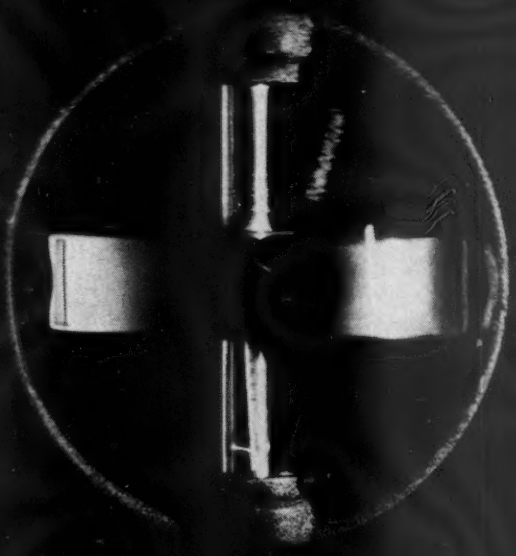
The patient allergic to certain foods may find holiday menus a temptation difficult to resist. When he yields to allergenic dishes, BENADRYL brings him prompt relief from gastrointestinal distress. BENADRYL also helps to control cutaneous reactions and respiratory symptoms so often associated with food sensitivity. BENADRYL Hydrochloride (diphenhydramine hydrochloride, Parke-Davis) is available in a variety of forms, including Kapseals,® 50 mg. each; Kapseals, 50 mg., with ephedrine sulfate, 25 mg.; Capsules, 25 mg. each; Elixir, 10 mg. per 4 cc.; and for delayed action, Emplets,® 50 mg. each. For parenteral therapy, BENADRYL Hydrochloride Steri-Vials,® 10 mg. per cc.; and Ampoules, 50 mg. per cc.

Parke, Davis & Company
Detroit 32, Michigan

92759



minimal disturbance
of the patient's chemical and psychic balance...



still unsurpassed for total corticosteroid benefits

Aris

Substantiated by published reports of leading clinicians:

- **effective control** of allergic and inflammatory symptoms[1-20]
- **minimal disturbance** of the patient's chemical and psychic balance[1,4,5,8-19]

stocort®

Triamcinolone LEDERLE

lt anti-inflammatory and antiallergic levels
ARISTOCORT means:

- **freedom from salt and water retention**
- **virtual freedom from potassium depletion**
- **negligible calcium depletion**
- **euphoria and depression rare**
- **no voracious appetite — no excessive weight gain**
- **low incidence of peptic ulcer**
- **low incidence of osteoporosis with compression fracture**

Indications: rheumatoid arthritis; arthritis; respiratory allergies; allergic and inflammatory dermatoses; disseminated lupus erythematosus; nephrotic syndrome; lymphomas and leukemias.

Precautions: With ARISTOCORT all traditional precautions to corticosteroid therapy should be observed. Dosage should always be carefully adjusted to the smallest amount which will suppress symptoms. After patients have been on steroids for prolonged periods, discontinuance must be carried out gradually.

Supplied: Scored tablets of 1 mg. (yellow); 2 mg. (pink); 4 mg. (white); 16 mg. (white).

Diacetate Parenteral (for intra-articular and intrasynovial injection). Vials of 5 cc. (25 mg./cc.).

List of References 1-20 supplied on request.

Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y.

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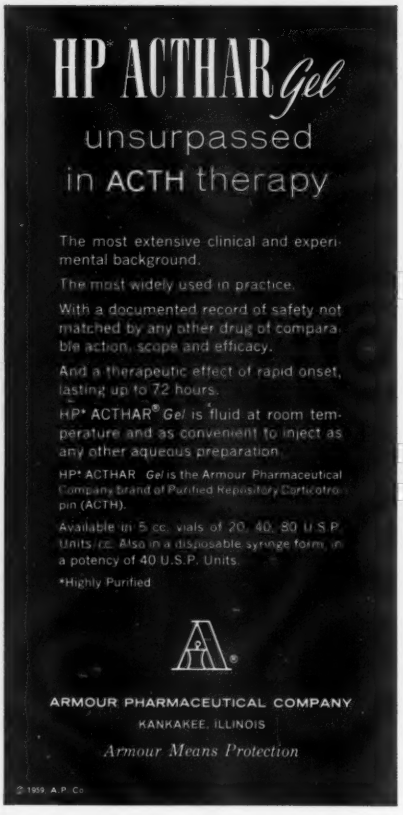
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unsurpassed
in ACTH therapy
The most extensive clinical and experimental background.
The most widely used in practice.
With a documented record of safety not matched by any other drug of comparable action, scope and efficacy.
And a therapeutic effect of rapid onset, lasting up to 72 hours.
HP* ACTHAR® Gel is fluid at room temperature and as convenient to inject as any other aqueous preparation.
HP* ACTHAR Gel is the Armour Pharmaceutical Company brand of Purified Repository Corticotropin (ACTH).
Available in 5 cc. vials of 20, 40, 80 U.S.P. Units/cc. Also in a disposable syringe form, in a potency of 40 U.S.P. Units.
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1 PINT
POLARAMINE®
EXPECTORANT
Caution: Federal law prohibits dispensing without prescription.
Each 5 cc (one teaspoonful) contains
Dexchlorpheniramine Maleate 2 mg.
d-Isoephedrine Sulfate 20 mg.
Glyceryl Guaiacolate 100 mg.
Sodium Benzoate (as preservative) 0.1%
Alcohol 1.5%
Usual Dose:
Adults—One to two teaspoonfuls three or four times a day.
Children—One-half to one teaspoonful three or four times a day
Professional literature available on request
Schering Corporation

YOU CAN EXPECT MORE FROM NEW POLARAMINE® EXPECTORANT

Because POLARAMINE Expectorant — Polaramine plus *d*-isoephedrine sulfate and glyceryl guaiacolate — Restores congested mucous membranes of the entire respiratory tract to normal...gently, rapidly...within only 15 to 30 minutes ■ Relieves unproductive coughing by increasing respiratory tract fluid output and by facilitating expectoration ■ Treats effectively the allergic components of respiratory illness ■ Is *delicious*...a new, different flavor.

POLARAMINE Expectorant is particularly valuable for the relief of coughs and complications of allergic conditions and the allergic manifestations of respiratory illnesses.

Each teaspoonful (5 cc.) of POLARAMINE Expectorant contains 2 mg. POLARAMINE Maleate (dexchlorpheniramine maleate), 20 mg. *d*-isoephedrine sulfate and 100 mg. glyceryl guaiacolate.

Dosage: Adults, 1 or 2 teaspoonfuls, 3-4 times daily; Children, ½ or 1 teaspoonful, 3-4 times daily.

Supply: 16 oz. bottles. SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY EN-1495-9

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OCCUPATIONAL ALLERGY *By* **European Academy of Allergy.** An ever increasing number of chemicals, many of them toxic, many of them allergenic, can be found not only in every factory and workshop, but in the hands of farmers, housewives, etc. Occupational allergy is now a problem of prime importance. This work illustrates the value of international cooperation and fills a long-time need for allergists and industrial medical officers to pool their knowledge. Here gathered together are the views of an authoritative group in a book which will change the outlook of both allergy and industrial medicine. **Almost every industry is considered,** such as baking, painting, pharmacy, textile manufacture, mining, etc. Special chapters on the skin as a defense organ and compensation for allergic diseases. Two unusual chapters on respiratory allergy in the medical profession and occupational eczema in therapists.

Publication date 1958 — 346 pages
$10.00 — 40 illustrations

INTERNATIONAL TEXTBOOK OF ALLERGY *Edited By* **J. M. Jamar,** *University Louvain.* A lifetime of experience with the allergic phenomenon would not enable one physician to write with competence on the varied phases of allergy presented here. The extensive field suggested—in fact, made imperative—a textbook written in cooperation. **Each chapter is presented by an internationally known authority in his particular field.** While many minds participated, the resulting volume is the epitome of uniformity and completeness, well edited, well organized. Progress in allergy is slow and calls upon qualities of the highest order. This text, **international in scope,** is designed for the physician whose goal is to master the many facets of its practice. **Encyclopedic** . . . invaluable to the allergist.

Publication date March 1959 — 640 pages
$17.50 — 93 illustrations

"ALLERGIC" ENCEPHALOMYELITIS: *Proceedings of a Symposium. Experimental "Allergic" Encephalomyelitis and Its Relation to Other Diseases of Man and Animals. Edited by* **Marian W. Kies,** *Chief, Section on Biochemistry, National Institute of Mental Health, Bethesda, Maryland; and* **Ellsworth C. Alvord, Jr.,** *Baylor University.* More than **60 authorities** who have done the significant work in this field took part in the symposium on which this work is based. Discussions built around twelve prepared speeches represent the heart of the book—bringing together the **latest information** concerning etiology and pathogenesis of allergic encephalomyelitis, both as produced in experimental animals by injection of brain-containing vaccines and as occurring in man following rabies-vaccine or other vaccine injections and exanthematous or other injections. **These distinguished scientists** 1) Examine critically whether any or all of these can really be considered due to allergic reaction 2) Evaluate the possible relation of these disorders to each other and to other diseases such as multiple sclerosis.

Publication date April 1959 — 590 pages
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in bronchial asthma

PREDNAMIN™ tablets "potentiated prednisone"

breaks the "side-effects barrier" to full, long-range corticosteroid benefits

PREDNAMIN brought excellent or good relief to 76% of 50 asthmatic patients . . . all of whom had responded unsatisfactorily to one or more years of specific therapy and to epinephrine, ephedrine and aminophylline. Although treatment was prolonged and continuous, only 2 patients required withdrawal of PREDNAMIN because of side effects.*

The optimally balanced PREDNAMIN combination magnifies the efficacy of small doses of prednisone . . . but leaves corticosteroid hazards at a low-dose minimum. With PREDNAMIN, problem asthmatics and patients with atopic and contact dermatoses need no longer be deprived of continuing and often dramatic corticosteroid benefits.

Each PREDNAMIN Tablet contains prednisone 2.5 mg., chlorprophenpyridamine maleate 2.0 mg., and ascorbic acid 250.0 mg. Bottles of 30 and 100.

*Swarts, H.: To be published.

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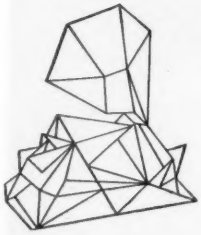
New York • Los Angeles • Montreal
World Leader in Dermatologicals

PURE ANTIHISTAMINE ACTION NOW A PHARMACOLOGIC FACT BECAUSE DĪSOMER SHEDS THE MOLECULAR DROSS

NEW...IN THE TREATMENT OF ALLERGIC DISORDERS



- *"...high therapeutic index"[1]*
- *unsurpassed clinical efficacy*
- *highly effective in exceptionally small doses*
- *side effects reduced to placebo level*

Disomer....a major scientific advance in the pharmacology of antihistamines!

DISOMER was described as being *"...as close to a pharmacologically pure form of histamine antagonist as the chemist can produce."*[1] Incorporating the newest knowledge of structure-function relationships, DISOMER comes closest thus far to the therapeutic ideal of pure antihistamine activity. DISOMER represents the *d*-isomer of racemic brompheniramine maleate. In shedding the *l*-isomer a high point in clinical effectiveness is achieved while side effects are reduced to the placebo level.

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With DISOMER your allergic patient remains your alert patient while enjoying unsurpassed freedom from allergic symptoms. Ready now for your prescription—DISOMER is available in a variety of dosage forms to fit your patients' individual requirements.

Availability:

DISOMER CHRONOTAB*	6 mg.
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DISOMER Tablets	2 mg.
DISOMER Syrup	2 mg. per 5 cc.

Usual dosage:

6 mg. CHRONOTAB	b.i.d.
4 mg. CHRONOTAB	t.i.d.
2 mg. Tablet	q.i.d.
Syrup 1 teaspoonful	q.i.d.

**Chronotab* is White's repeat-action tablet.*

References: (1) Gould, A. H. and Long, D. L.: Clinical Pharmacology and Therapeutic Use of Dexbrompheniramine Maleate (Disomer), a new Histamine Antagonist (submitted for publication). (2) Medical Department, White Laboratories, Inc.

WHITE LABORATORIES, INC.
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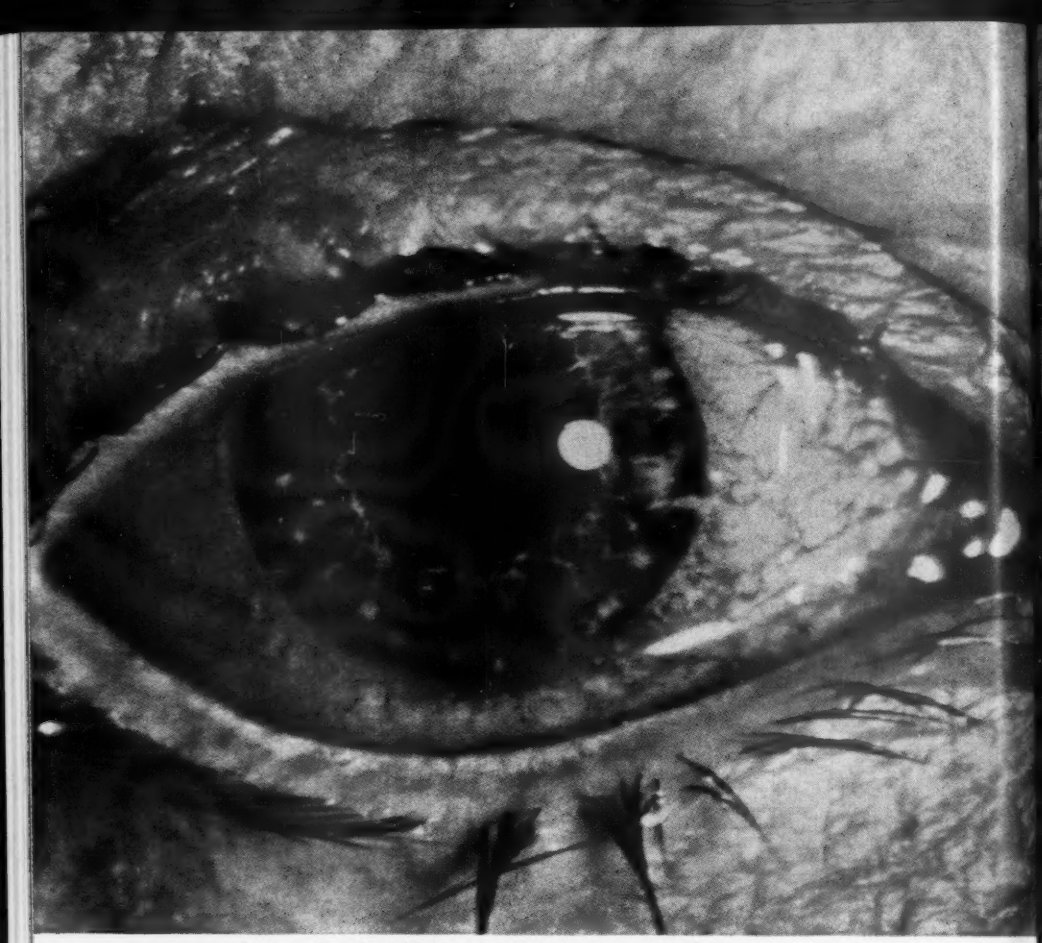
DEXBROMPHENIRAMINE MALEATE

...sheds the molecular dross



Acute conjunctivitis[1] before treatment, showing engorged irregular superficial vessels

NOW...the true solution for fast anti-inflammatory response and no irritating steroid particles

- mg. for mg. the most active steroid topically—up to 40 times the potency of hydrocortisone
- optimal not minimal steroid concentration in true solution for peak effectiveness . . . maximal contact at the site of the lesion
- quick-acting broad antimicrobial activity when infection threatens recovery
- superior patient comfort—no stinging, no irritating particles, bland carrier

1. Gordon, D. M.: Scientific Exhibit, American Medical Association, Annual Meeting, San Francisco, 1958.

4 days after treatment ACTUAL CLINICAL PHOTOGRAPHS

OPHTHALMIC SOLUTION

NeoDecadron*

DEXAMETHASONE 21-PHOSPHATE—NEOMYCIN SULFATE

INDICATIONS: Trauma—mechanical, chemical or thermal; conjunctival, corneal, or uveal tract inflammation involving the anterior segment; allergy; blepharitis.

DOSAGE: NeoDECADRON Ophthalmic Solution (0.1%)—One drop 4-6 times daily.

NeoDECADRON Ophthalmic Ointment (0.05%)—Applied 3-4 times daily.

In severe or sight-threatening conditions, the frequency of administration may be increased. Systemic therapy with DECADRON Tablets may be prescribed adjunctively.

PRECAUTION: Steroid therapy should never be employed in the presence of tuberculosis or herpes simplex.

Additional information is available to physicians on request.

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Division of Merck & Co., Inc. • Philadelphia 1, Pa.

Product	Steroid Concentration	active ingredients: Dexamethasone 21-Phosphate (as the disodium salt)	active ingredients: Neomycin Sulfate	Supplied
NeoDECADRON Ophthalmic Solution	0.1%	1 mg./cc.	5 mg./cc. (equivalent to 3.5 mg. neomycin base)	5 cc. (¼ oz.) sterile dropper-bottles
DECADRON Phosphate Ophthalmic Solution	0.1%	1 mg./cc.	—	5 cc. (¼ oz.) sterile dropper-bottles
NeoDECADRON Ophthalmic Ointment	0.05%	0.5 mg./Gm.	5 mg./Gm. (equivalent to 3.5 mg. neomycin base)	3.5 Gm. (⅛ oz.) tubes
DECADRON Phosphate Ophthalmic Ointment	0.05%	0.5 mg./Gm.	—	3.5 Gm. (⅛ oz.) tubes

prescribe DeVILBISS for EFFECTIVE AEROSOL THERAPY

Abundant evidence attests to the therapeutic efficacy of DeVilbiss aerosol therapy equipment in the treatment of bronchial asthma, chronic bronchitis, bronchiectases and other respiratory problems.

DeVilbiss nebulizers produce particles of suitable and effective size to reach all recesses of the lungs and bronchi.

When you prescribe Aerosol Therapy for your patient, prescribe DeVilbiss Nebulizers . . . there are models available for continuous, intermittent or occasional treatment periods.

Rubber stopper protects solution, prevents spilling.

Removal of this stopper increases delivery rate.

Hand-blown glass vaporizing tubes . . . no contamination from metal.

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NO. 640 Nebulizer combination. Retail complete $6.50.

DeVilbiss
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Since 1888 three generations of physicians have used and prescribed DeVilbiss products.

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dust
a major offender

Dust is a principal offender in allergies of the respiratory tract. It cannot be avoided — and the dust-allergic patient requires medical attention. POLARAMINE — the closest to a perfect antihistamine — is the closest to a perfect solution for the problem of the patient suffering from irritating nonseasonal allergens. POLARAMINE offers swift, sure, safe action with these outstanding advantages —

▪ Therapeutically effective at lower dosages than other antihistamines ▪ Highest therapeutic index of all antihistamines (3380) ▪ Fewer side effects than with other antihistamine preparations ▪ Highly efficacious — a single POLARAMINE REPETAB gives your patient all-day or all-night protection from discomfort of allergic symptoms

POLARAMINE REPETABS

PROMPT REPETAB RELIEF · LASTS ALL DAY OR NIGHT ·

symbol of the one-dose convenience you want for your patient

SUPPLY: POLARAMINE REPETABS, 6 mg., bottles of 100 and 1000 / POLARAMINE REPETABS, 4 mg., bottles of 100 and 1000 / Tablets, 2 mg., bottles of 100 and 1000 / Polaramine Syrup, 2 mg./5 cc., bottles of 16 oz.

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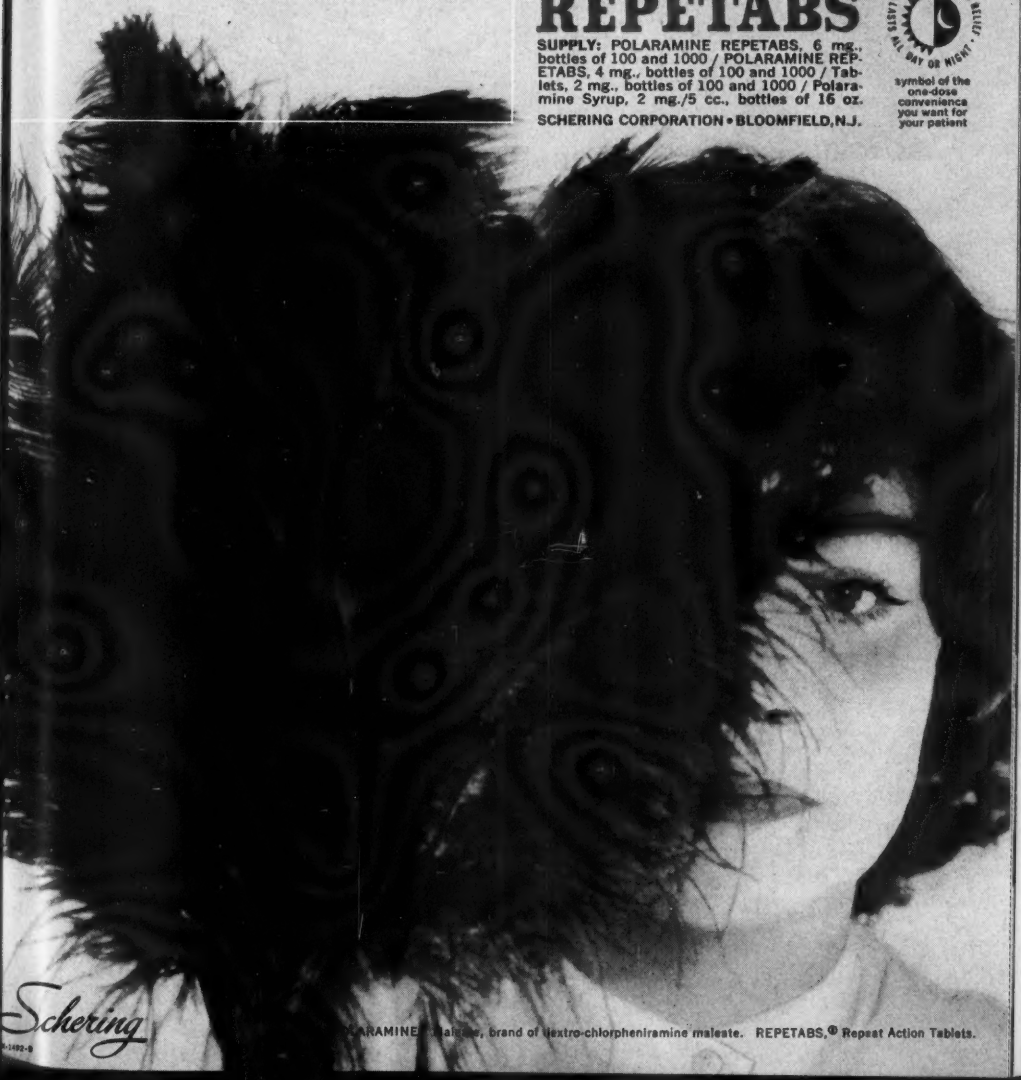

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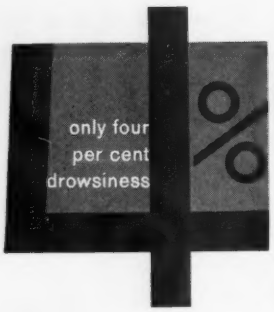
POLARAMINE, brand of dextro-chlorpheniramine maleate. REPETABS,® Repeat Action Tablets.

In head colds, bronchitis and sinusitis,

81% good to excellent symptomatic relief

with S.K.F.'s new antihistamine preparation



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brand of diphenylpyraline hydrochloride

Spansule® 5 mg. and Tablets 2 mg.

brand of sustained release capsules

Of 366 patients treated with 'Hispril' in pre-introduction clinical trials for a variety of upper respiratory infections, 297 (81%) obtained good to excellent symptomatic relief. Conditions studied included bronchitis, sinusitis, rhinitis and postnasal drip.

Prescribe 'Hispril' to relieve such allergic symptoms as nasal stuffiness and congestion, whether associated with allergic rhinitis or upper respiratory infection. In either case, a single 'Hispril' *Spansule* capsule often relieves sneezing and reduces nasal secretions—yet leaves the patient active and alert all day long.

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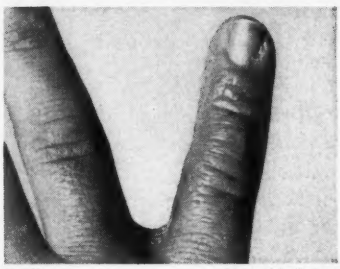
for total management of itching,[1,2] inflamed,[3,4] infected[5,6] skin lesions

Dermatitis repens [with staph and monilia] 7 weeks duration



Cleared in 5 days

new Mycolog ointment

Kenalog, Spectrocin and Mycostatin in Plastibase

antipruritic/anti-inflammatory/antibacterial/antifungal

Mycolog Ointment — containing the new superior topical corticoid Kenalog — reduces inflammation,[3,4] relieves itching,[1,2] and combats or prevents bacterial, monilial and mixed infections.[5-7] It is extremely well tolerated, and assures a rapid, decisive clinical response for most infected dermatoses.

"Thirty-one of 38 patients... obtained excellent or good control of dermatological lesions... [Mycolog] was highly effective, particularly in the management of mixed infections. Several recalcitrant eruptions which had not responded to previous therapy were remarkably responsive to the daily application of this preparation over periods of 2 to 3 weeks."[5]

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Application: Apply 2 to 3 times daily. Supply: 5 Gm. and 15 Gm. tubes. Each gram supplies 1.0 mg. (0.1 %) triamcinolone acetonide, 2.5 mg. neomycin base, 0.25 mg. gramicidin, and 100,000 units nystatin in PLASTIBASE.

References: 1. Shelmire, J. B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T. E., Jr., and Derbes, V J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R. C. V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T. H.:Newcomer, V. D., and Reisner, R. M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R. F., and Hallett, J. J.: Monographs on Therapy 3:153 (Nov.) 1958. • 6. Smith, J. G., Jr.; Zawisza, R.J., and Blank, H.: Monographs on Therapy 3:111 (Nov.) 1958. • 7. Monographs on Therapy 3:137 (Nov.) 1958. • 8. Howell, C. M., Jr.: North Carolina M. J. 19:449 (Oct.) 1958. • 9. Bereston, E. S.: South, M. J. 50:547 (April) 1957.

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Squibb Quality — the Priceless Ingredient

'SPECTROCIN'®, 'MYCOSTATIN'®, 'PLASTIBASE'®, 'MYCOLOG' AND 'KENALOG' ARE SQUIBB TRADEMARKS

CREAM OF RICE IS MOST HYPOALLERGENIC

In an intensive study of 174 unselected children, not one single case of intolerance to cooked rice was discovered. After judging this study and comparative reports on sensitivity to cereals, it was concluded that "rice shows the fewest allergic reactions of any cereal checked . . . even children potentially allergic to rice tolerate it well when it is cooked in the presence of moisture."

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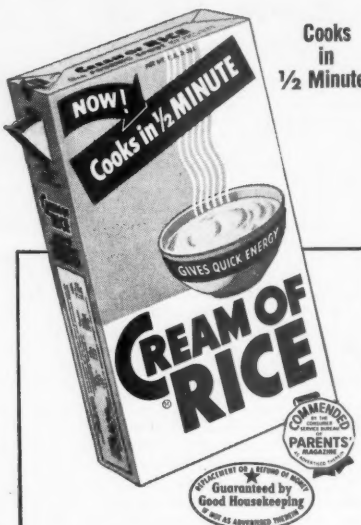
NEW CLINICAL EVIDENCE

Results of new Medical Study prove that *Cream of Rice is easier to digest than any other kind of cereal!* Gives quick food energy, too! It is non-allergenic, low in sodium, low in fat, but rich in Vitamin B_1, Riboflavin, Niacin and Iron. That is why it is especially recommended for people who suffer from sensitive stomachs, high blood pressure, ulcers and other digestive ailments.

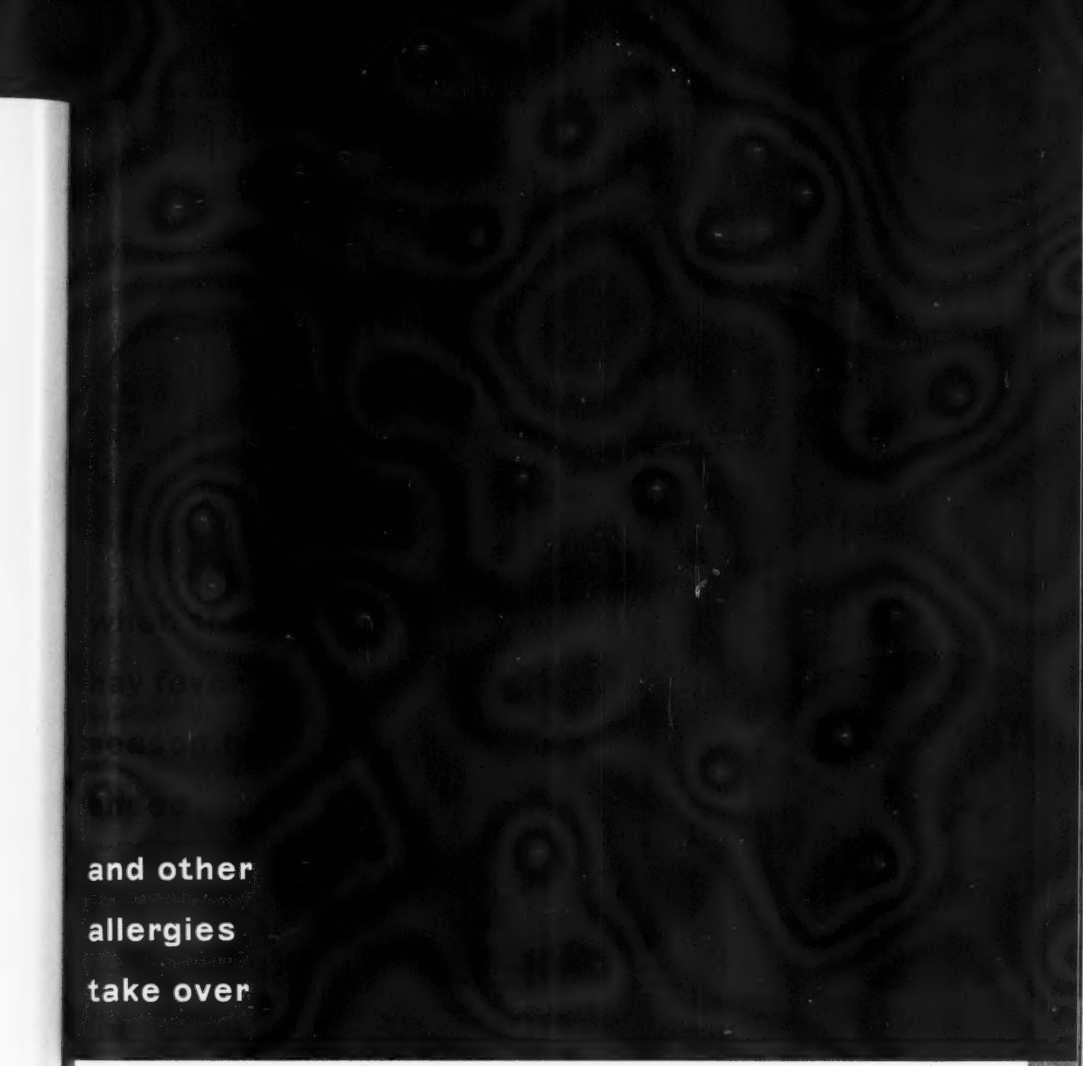
RECOMMENDED FOR BABIES AND GROWING CHILDREN, TOO!

Child specialists recommend Cream of Rice as one of baby's first solid foods because it's *easier to digest than any other kind of cereal.* Cream of Rice also is recommended for growing children because it's so rich in food value.



Cooks in ½ Minute!

Write for Professional Samples to: Grocery Store Products Co., Dept. C12AA, West Chester, Pa.



METRETON

"Meti" steroid-antihistaminic

for rapid relief systemically—METRETON Tablets—
in drug reactions, urticaria, angioedema, atopic and contact dermatitis, allergic eczema, ocular allergies, serum sickness

topically for allergic rhinitis—METRETON Nasal Spray

topically for eye allergies—
METRETON Ophthalmic Suspension

supplied

METRETON® **Tablets,** bottles of 30 and 100. Each METRETON Tablet contains 2.5 mg. prednisone, 2 mg. chlorprophenpyridamine maleate, and 75 mg. ascorbic acid.

METRETON **Nasal Spray,** 15 cc. squeeze bottle. Each cc. of METRETON Nasal Spray contains 2 mg. (0.2%) prednisolone acetate and 3 mg. (0.3%) chlorprophenpyridamine gluconate.

METRETON **Ophthalmic Suspension,** 5 cc. dropper bottle. Each cc. of METRETON Ophthalmic Suspension contains 2 mg. (0.2%) prednisolone acetate and 3 mg. (0.3%) chlorprophenpyridamine gluconate.

Meti,® brand of corticosteroids.

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5-312

Contents for November-December, 1959

BUCCAL AMYLASE

Buccal amylase was found to abrogate coincidental allergic manifestations while being applied as an "anti-inflammatory" agent. A mast-cell discharge theory is proposed to account for systemic effects of depolymerizing enzymes.

Carlos Tejo, M.D., Joaquin C. Bido, M.D., Simon Tomasini, M.D., and *Robert D. Barnard, M.D.* (Departments of Pathology and Surgical Research, Harlem Hospital, New York City Department of Hospitals), New York, New York 855

REHABILITATION OF CHILDREN WITH INTRACTABLE ASTHMA

W. B. Steen, M.D., F.A.C.A., Tucson, Arizona 864

ALLERGY AND RECURRENT EPISTAXIS IN CHILDREN

Donald H. Walker, M.D., F.A.C.A. (Department of Otolaryngology, Sharon General Hospital), Sharon, Pennsylvania 872

DURATION OF EFFECT OF A SUSTAINED RELEASE MIXTURE OF ANTIHISTAMINIC AGENTS: TRIDECAMINE

Tridecamine Dospan, a new sustained-release triple antihistaminic preparation, was evaluated on the basis of its duration of effect. The results of this study confirm the fact that Tridecamine is long-acting and maintains its effect over a twelve to fourteen-hour period.

T. L. Jones, M.D., L. B. Dale, Ph.D., and *G. L. Christenson, B.S.,* Cincinnati, Ohio 878

PRELIMINARY STUDY OF USE OF BUCCAL PROTEASE THERAPY IN BRONCHIAL ASTHMA

In older chronic bronchial asthmatic patients the infectious component can be better destroyed by the use of buccal proteases in conjunction with antibiotics and hyposensitization.

Donald B. Frankel, M.D., F.A.C.A.; Abe B. Aaronson, M.D., F.A.C.A., and *Norman J. Ehrlich, M.D., F.A.C.A.,* Chicago, Illinois 883

DEXAMETHASONE IN CHILDHOOD ASTHMA

Dexamethasone was found effective in controlling symptoms in 21 intractable asthmatic children and 1 asthmatic child, who also suffered from rheumatic pericarditis, at the Jewish National Home for Asthmatic Children.

Constantine J. Falliers, M.D., and *Samuel C. Bukantz, M.D.,* (Jewish National Home for Asthmatic Children, and Children's Asthmatic Research Institute and Hospital), Denver, Colorado 887

Dexamathesone in Dermatologic Therapy

Orally administered Dexamethasone is a potent anti-inflammatory drug when used in the treatment of some dermatologic disorders. It is also effective topically in treating second degree burns and certain skin lesions.

Perry A. Sperber, M.D., F.A.C.A. (Director of the Dermatology and Allergy Clinic, Halifax District Hospital), Daytona Beach, Florida..... 895

Constitutional Reaction Following Buccal Trypsin

A patient, with urticaria, who developed severe asthma and vascular collapse following buccal trypsin, is reported. A tuberculin type antibody with positive passive transfer against trypsin was demonstrated. Antibodies against trypsin have not been previously reported.

Irvin Caplin, M.D., F.A.C.A., George F. Parker, M.D., F.A.C.A., John T. Haynes, M.D., and *Harvey Meulbroek, M.D.* (Allergy Clinic of Methodist Hospital), Indianapolis, Indiana..... 901

Possible Allergic Conditions Affecting the Central Nervous System Viewed from a Neurological Standpoint

Robert B. Aird, M.D. (Professor and Chairman, Department of Neurology, University of California School of Medicine), San Francisco, California.... 905

Evaluation of Effectiveness, Dosage and Toxicity of "Para-Bromdylamine Maleate" in Allergic Rhinitis of Infants and Children

John P. McGovern, M.D., F.A.C.A., Thomas R. McElhenney, M.D., Thomas R. Hall, M.D., and *Kenneth D. Burdon, Ph.D., F.A.C.A.* (Baylor University College of Medicine), Houston, Texas..... 915

The Centennial of Pollen Aerobiology

A short review of the development of apparatus and methods for measuring the pollen content of outdoor air. Volumetric sampling devices of practical accuracy for allergists may soon replace gravity slide tests.

Oren C. Durham (Chairman, Pollen and Mold Committee, Research Council, American Academy of Allergy), Angwin, California..... 923

Anaphylaxis Reactions with Purified Proteins from Milk (Historical Document)

H. Gideon Wells and *Thomas B. Osborne,* New Haven, Connecticut..... 930

Papers of Interest..... 941

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1. Schluger, J. et al.: Am. J. Med. Sci. 233:296, 1957.
2. Bradwell, E. K.: Acta med. scand. 146:123, 1953.
3. Truitt, E. B. et al.: J. Pharm. Exp. Ther. 100:309, 1950.

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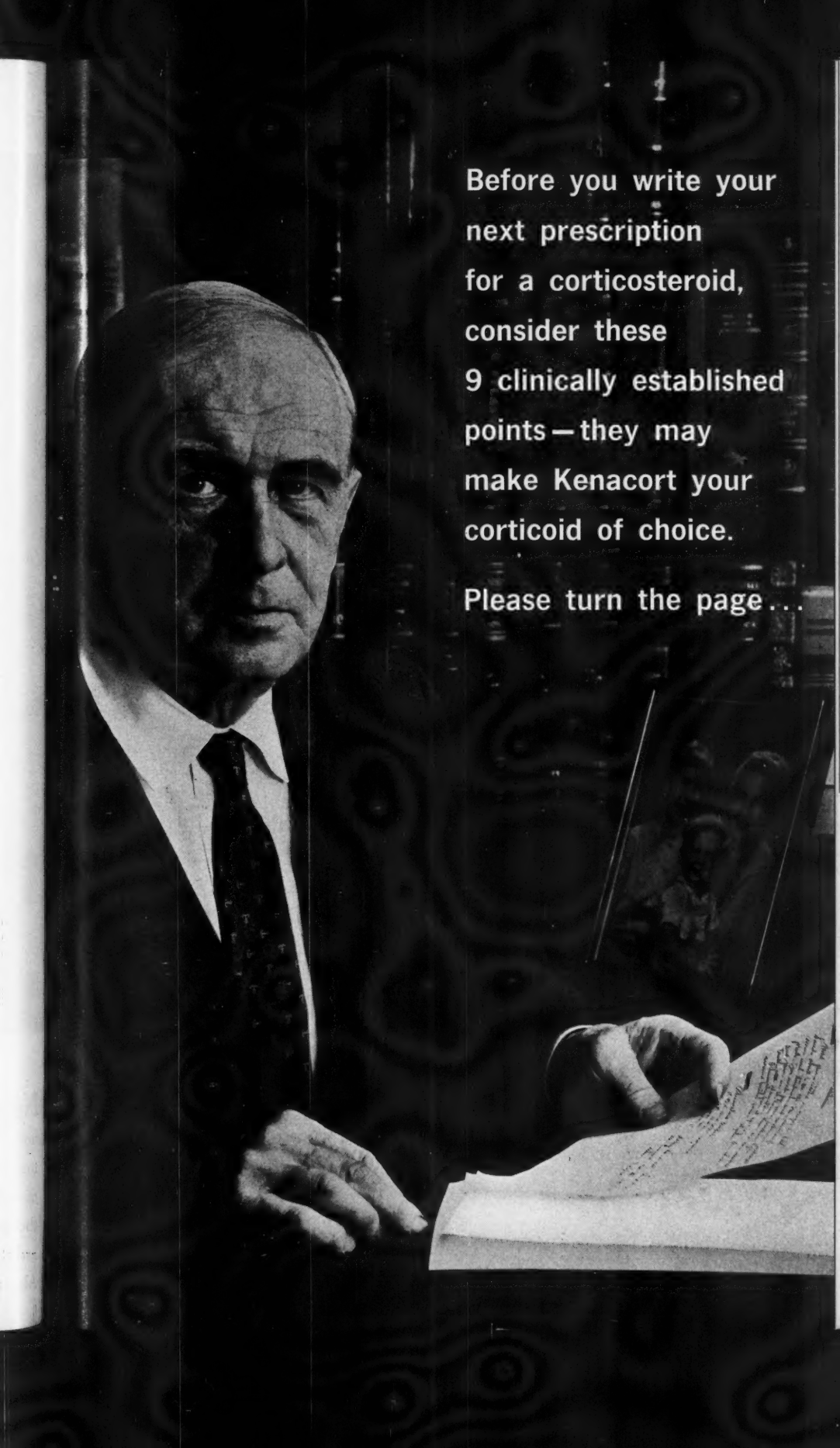
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Allison, J. R., Sr., and Allison, J. R., Jr.:
Monographs on Therapy 3:99 (Oct.) 1958.

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continuing therapy—maintenance doses are low

Feinberg, S. M.; Feinberg, A. R., and Fisherman, E. W.:
J. A. M. A. 167:58 (May 3) 1958.

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Hartung, E. F.:
J. A. M. A. 167:973 (June 21) 1958.

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Council on Drugs:
J. A. M. A. 169:257 (Jan. 17) 1959.

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Bongiovanni, A. M.; Mellman, W. J., and Eberlein, W. R.:
J. Pediat. 53:3 (July) 1958.

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Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.:
J. A. M. A. 167:959 (June 21) 1958.
Bernsten, C. A., Jr., and others:
New York Rheumatism Association, Annual Meeting,
New York, April 9, 1959.

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J. A. M. A. 167:959 (June 21) 1958.
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J. A. M. A. 169:257 (Jan. 17) 1959.

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Hartung, E. F.:
J. A. M. A. 167:973 (June 21) 1958.

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(1) Silbert, N. E., Ciba Clinical Symposia; 6: 86: May 1954
(2) Mechanick, I., Annals of Allergy; 12: 164: March 1954
(3). Rosen, F. L., J. Med. Soc. N.J., 51: 110: March 1954

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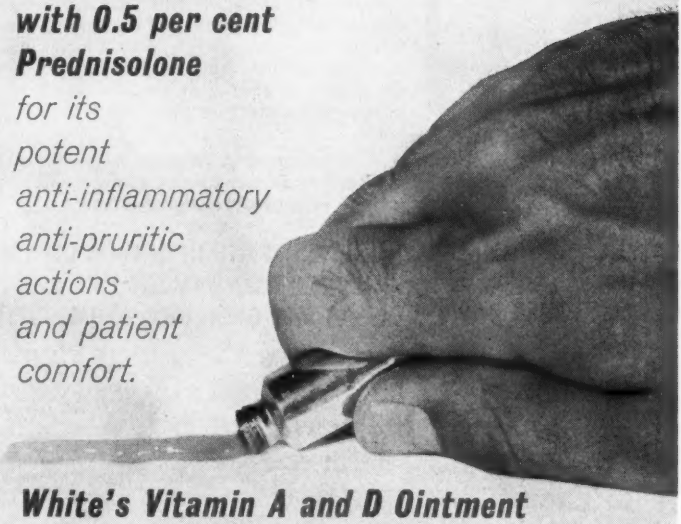

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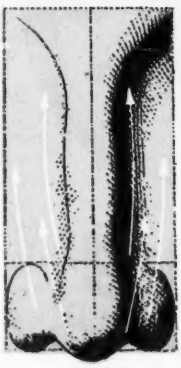

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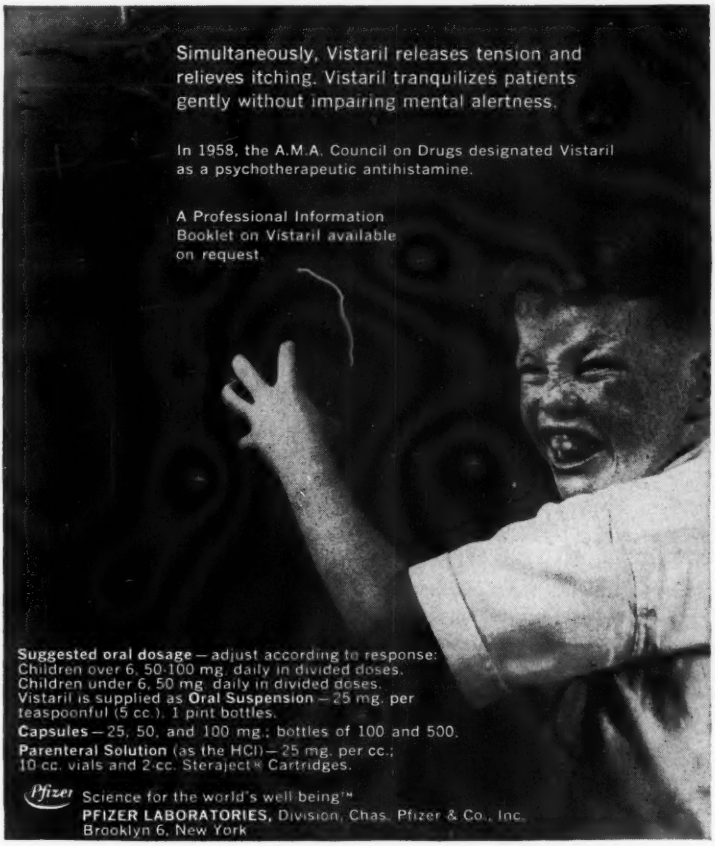
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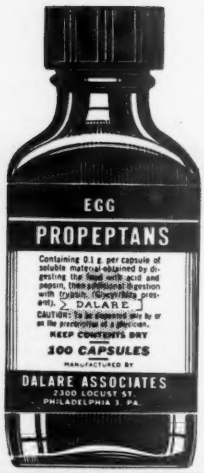
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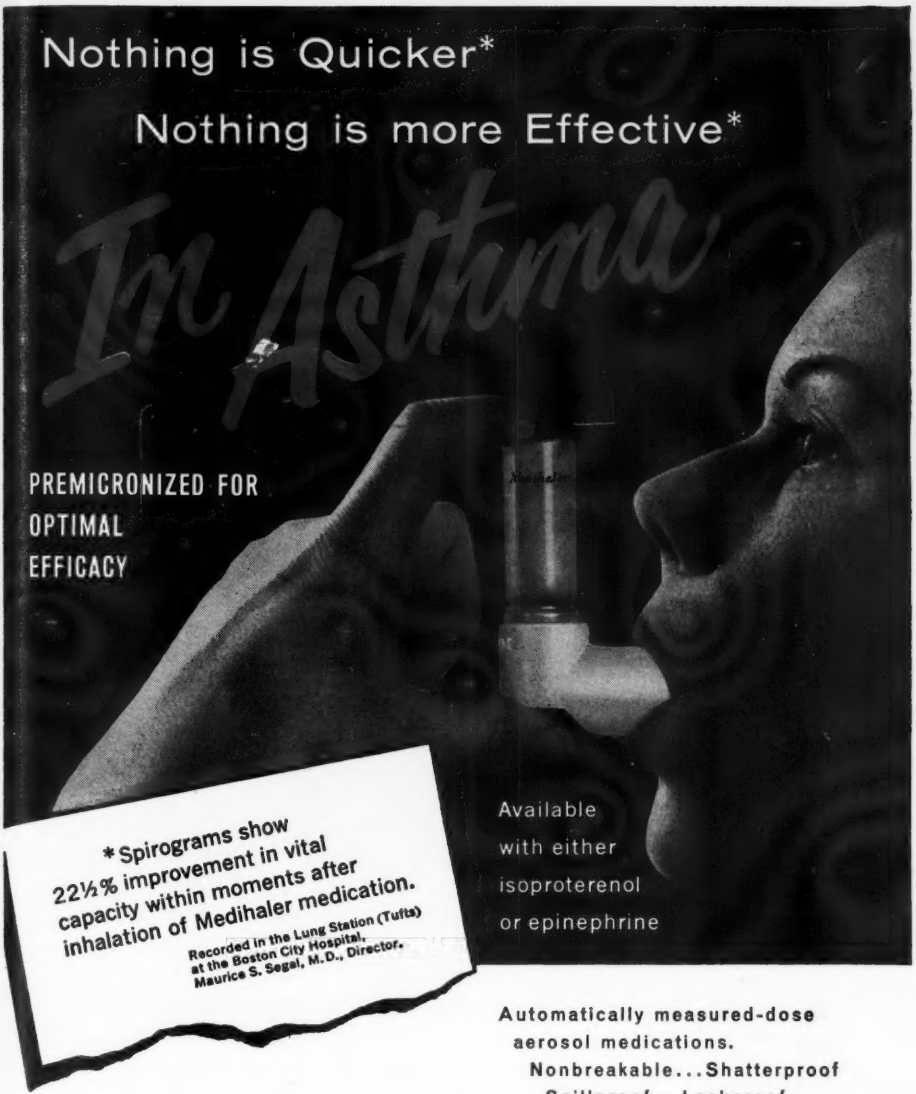
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1. Shane, S. J., Krzyski, T. K., and Copp, S. E.: Canad. M.A.J. 77:600 (Sept. 15) 1957.

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1. Spielman, A. D.: New York J. Med. *55*:1603 (June 1) 1955.
2. Shinefield, M. A.: New York J. Med. *56*:1466 (May 1) 1956.
3. Dalven, J., and Romano, F. J.: New York J. Med. *57*:1748 (May 15) 1957.
4. Gundy, J. E.: J. Pediat. *51*:516 (Nov.) 1957.
5. Spielman, A. D.: A.M.A. Arch. Otolaryng. *67*:204 (Feb.) 1958.

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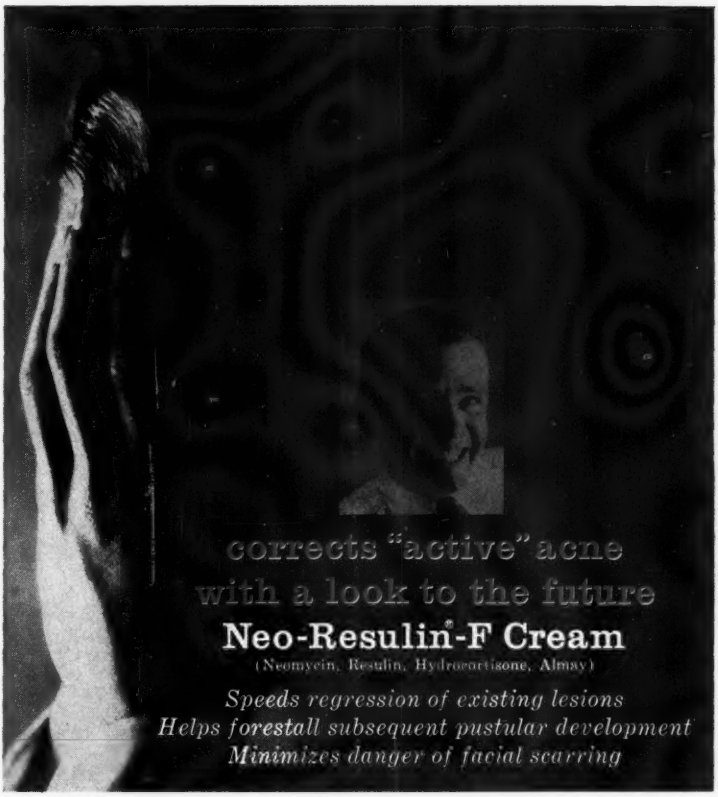
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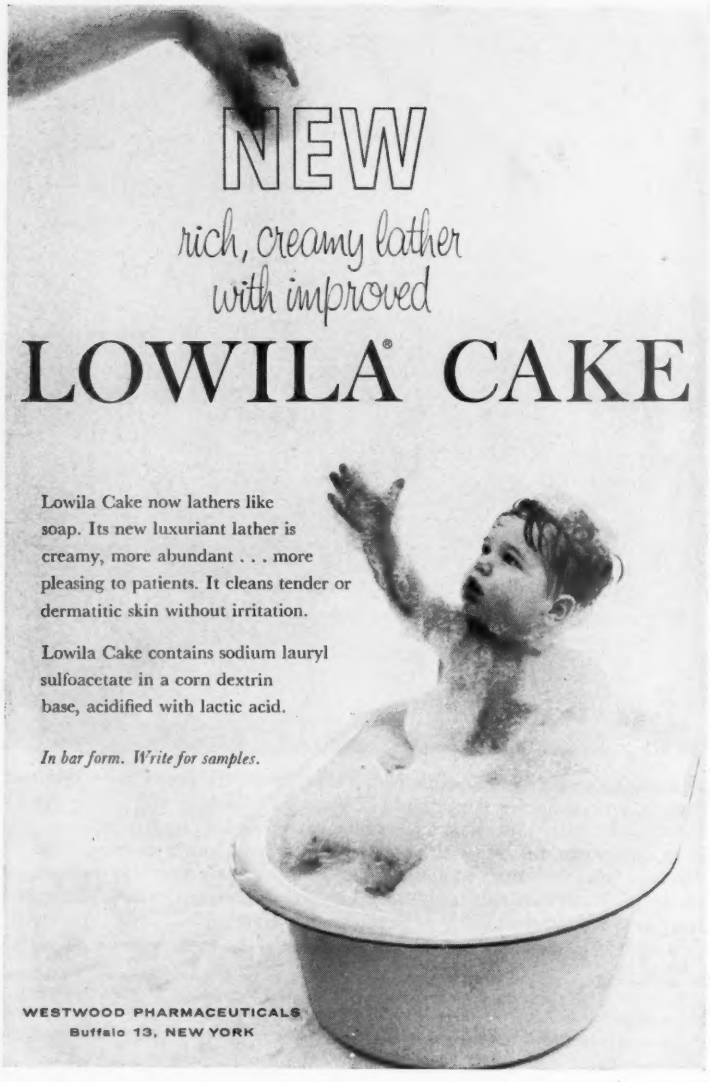
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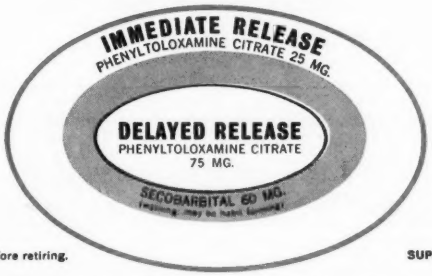

DOSAGE: 1-2 tablets before retiring.

SUPPLIED: Bottles of 100.

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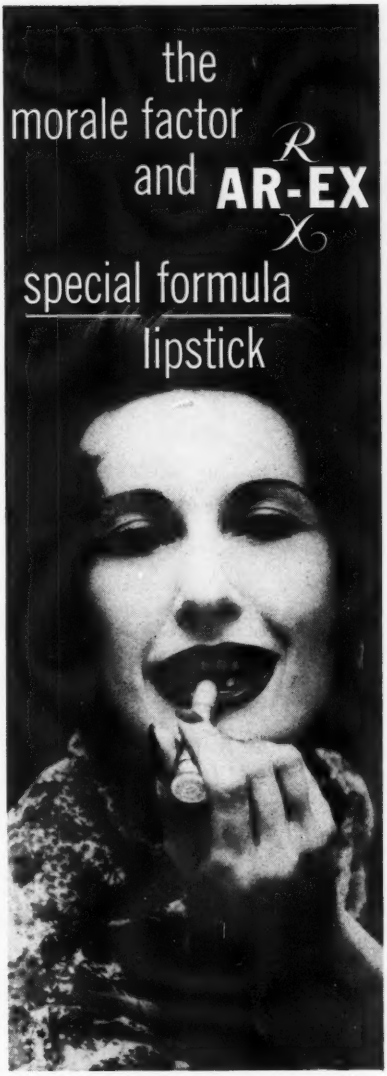

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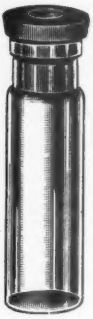

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1. Miller, H., and Baruch, D.: Practice of Psychosomatic Medicine as Illustrated in Allergy, Blakiston Company, 1956. 2. Swartz, H.: Ephoxamine in the Symptomatic Treatment of Bronchial Asthma, Current Therapeutic Research, 1 (Nov.) 1959.

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